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CARDIAC MANIFESTATIONS OF FRIEDREICH'S ATAXIA*

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SINCE Friedreich's original description[1] of 6 cases of familial hereditary ataxia in 1863, numerous papers have been written on this subject. The vast majority of these elaborate on the neurologic and pathological features of the disease.

There are few reports of cardiac manifestations in Friedreich's disease, and almost all of them have appeared in publications concerned primarily with the circulation; hence, it seems worth while to draw the attention of physicians in general to this aspect of the syndrome. We are presenting 6 cases of Friedreich's ataxia with cardiac changes that were seen within the past few years at the Children's Medical Center of Boston. The autopsied case is the only one of its kind in the files of the Children's Hospital and the Peter Bent Brigham Hospital. Another report of it, from the pathological viewpoint,[2] is currently in publication.

CASE REPORTS

CASE 1. R. S., a 6-year-old boy, was admitted to the Children's Hospital in 1937 with a history of unsteady gait of 2 years' duration. The diagnosis of Friedreich's ataxia was made on the basis of nystagmus, slurred speech, ataxia, absent knee jerks and ankle jerks, equinovarus and scoliosis. The family history, however, was negative for this disease.

During his stay in the hospital, it was noted by physical and x-ray examination that his heart was enlarged. A systolic murmur was heard over the left second interspace. No electrocardiogram was taken. The boy was transferred to the Massachusetts Hospital School in Canton, Massachusetts, where a large number of such patients are treated. He stayed there for more than 10 years. In 1948, he developed an upper respiratory infection, fever, cough, dyspnea and cyanosis. A diagnosis of pneumonia was made. After a week's illness he died.

Post-mortem examination, performed in the Pathology Department of the Children's Hospital, showed scoliosis, flexion deformities and bilateral equinovarus. In the central nervous system the changes characteristic of Friedreich's ataxia were found. The heart was enlarged mainly in the region of the left ventricle. Microscopical examination revealed extensive fibrosis in all areas. The few remaining muscle fibers showed extensive fatty degeneration (Fig. 1). The coronary arteries were found to have marked medial hypertrophy, intimal proliferation and varying degrees of obstruction (Fig. 2). The lungs showed bronchial pneumonia, edema and congestion.

FIGURE 1. *Section of Remaining Muscle Fibers in Case 1, Showing Fatty Degeneration.*

CASE 2. L. D., a 4½-year-old boy, was admitted to the Children's Hospital in January, 1949, with two sets of complaints: increasing dyspnea and hacking cough of 1 year's duration, and progressive unsteadiness of gait for the same period.

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The family and past histories were not remarkable. Physical examination revealed him to be underdeveloped. He showed the characteristic features of Friedreich's ataxia — equinovarus and absent knee and ankle jerks. The heart was grossly enlarged. The heart sounds were distant. Extrasystoles were frequent. A soft Grade 3 systolic murmur was heard best at the apex, and was transmitted to the axilla and back. The liver edge extended 4 cm. below the right costal margin at the nipple line.

Examination of the blood revealed a red-cell count of 4,800,000, with a hemoglobin of 12.5 gm., and a white-cell count of 11,200 to 13,200. The total protein was 7.42 gm. per 100 cc. The sedimentation rate was 8 mm. per hour by the Westergren method. Blood Hinton and tuberculin tests were negative.

FIGURE 2. *Typical Example of the Widespread and Severe Coronary-Artery Obstruction in Case 1.*

Roentgenograms showed generalized enlargement of the heart. Fluoroscopic examination revealed rather weak cardiac pulsations. An electrocardiogram (Fig. 3) disclosed normal sinus rhythm and rate, ectopic ventricular complexes, depressed ST segments, and diphasic to negative T waves in the three standard limb leads. A QR wave and an inverted T wave were present in Lead aVF. The chest leads showed inverted T waves in Leads V_5 and V_6, with a depressed ST segment in Lead V_6. A longer electrocardiographic tracing of Lead 2 (Fig. 4) revealed that the ectopic ventricular complexes occurred with identical configuration and with a distinct rhythm of their own at a rate of 24 per minute, thus constituting a ventricular type of parasystole.

On March 10, a liver biopsy was taken, which showed no changes suggestive of glycogen-storage disease. On March 16, exploratory thoracotomy was performed by Dr. Robert E. Gross. About 600 cc. of clear, straw-colored fluid was removed from the pericardial sac. The heart felt hypertrophied to the examining finger, and looked enlarged even after removal of the fluid. Postoperative electrocardiograms showed the same abnormalities as those noted before the operation, indicating that the pericardial fluid was not the main cause of the electrocardiographic changes.

Since the thoracotomy, the patient has been doing fairly well. His circulatory complaints have diminished greatly. However, his neurologic condition remains unchanged, with a considerable degree of ataxia. Since discharge from the Children's Hospital, he has experienced at least four episodes of chest pain. These were not related to exertion, and subsided spontaneously in a few minutes without the use of nitroglycerin. During two of these attacks, a sharply demarcated area of mottling appeared on the left side of the chest near the axilla. The latest roentgenograms and electrocardiogram, taken 1 year after he was first seen, still show pronounced changes, much the same as those noted postoperatively.

CASE 3. E. C., a 13½-year-old girl, was admitted to the Children's Hospital in February, 1947, with the chief complaint of inability to walk since the age of 7 years. The family history was noncontributory. Physical examination showed marked ataxia, severe scoliosis, weakness, halting speech, and absent knee and ankle jerks. The heart seemed entirely normal, except for a Grade 2 systolic murmur found in the second left interspace. X-ray films of the chest showed no cardiac enlargement. An electrocardiogram (Fig. 5) revealed an inverted T wave in Lead 1, a diphasic T wave in Lead 2, and a tall R wave in Lead aVF, with diphasic and inverted T waves in Leads V_4 to V_6.

It is interesting to note that the diagnosis of Friedreich's disease did not seem reasonable at the time of hospital admission. A cerebellar neoplasm was suspected — so seriously that extensive neurologic studies were made, including electroencephalograms, pneumoencephalograms, ventriculograms and bilateral burr-holes — all with negative results.

CASE 4. E. W., a 12-year-old boy, was first seen at the Children's Hospital in September, 1946, at the age of 7 10/12 years, with the chief complaint of trouble in walking since the age of 2 years. The family history revealed two siblings with Friedreich's disease. On physical examination, the patient presented characteristic findings of Friedreich's ataxia, including cavus deformity of the foot, scoliosis, ataxia, positive Romberg sign and absent knee and ankle jerks. The heart seemed entirely within normal limits, except for a Grade 2 systolic murmur audible over the pulmonic area.

The diagnosis having been established without question, he was transferred to the Massachusetts Hospital School in Canton, Massachusetts, where physical examination was the same as at the Children's Hospital. An x-ray film of the chest demonstrated no cardiac enlargement. An electrocardiogram (Fig. 6) showed inverted T waves in Leads 1 and 2, a tall R wave with inverted T wave in Lead aVF, and inverted T waves in Leads V_1 to V_5 with a diphasic T wave in Lead V_6.

CASE 5. J. C., an 11-year-old girl, was first admitted to the Children's Hospital at the age of 5¼ years in September, 1944. Her chief complaint was inability to walk of 1 year's duration. The family history was noncontributory.

Physical examination showed absent knee and ankle jerks, scanning speech, positive Romberg sign, gross intention tremor and generalized weakness. A cerebellar lesion was suspected at first, and she was therefore subjected to a thorough neurologic investigation, including electroencephalograms, pneumoencephalograms and bilateral burr-holes. These studies failed to reveal any abnormality of the cerebellum. The heart at this time was described as entirely normal on physical examination.

The second admission was 2½ years later, at the age of 8 years, with the same chief complaints as before, except that the intention tremor was more marked. At this time physical examination and x-ray films showed the heart to be enlarged, the border of cardiac dullness extending to the left. On auscultation the pulmonic second sound seemed accentuated, and a Grade 3 pulmonic systolic murmur was

also discovered. The pulse was irregular, with a rate of 96 per minute. Standard-limb-lead electrocardiograms revealed sinus arrhythmia and inverted T waves in Leads 1 to 3. On the basis of the marked intention tremor, the appearance of a heart murmur, electrocardiographic changes and cardiac enlargement, the tentative diagnosis of chorea with rheumatic heart disease was made. The patient had no fever throughout her hospital stay; the sedimentation rate was always normal, and the PR intervals were never prolonged.

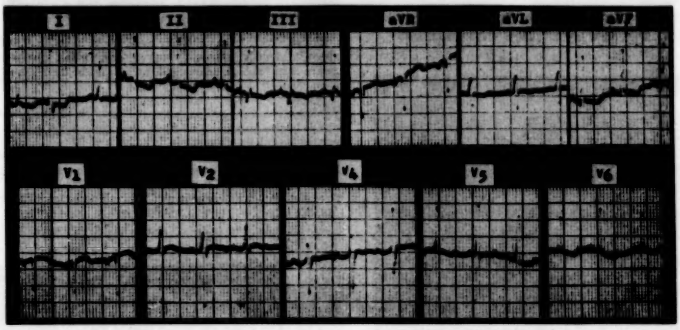

FIGURE 3. *Electrocardiogram in Case 2 Taken Shortly after Hospital Admission, Showing the Abnormal T Waves in All Leads, with Some ST Segment Depressions.*
An ectopic beat is also shown in Lead 1.

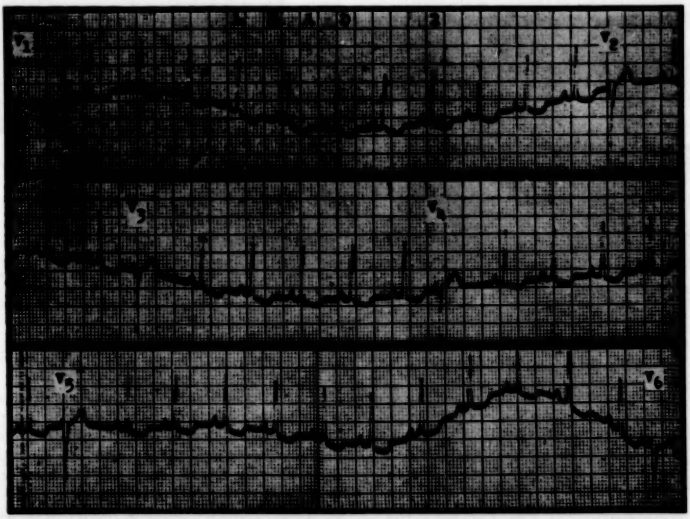

FIGURE 4. *A Continuous Record on Lead 2 Disclosing the Ventricular Parasystolic Focus, with a Rate of Approximately 24 per Minute.*
Note the long interval between ectopic beats in Leads V_1 and V_3, which is an exact multiple of the usual interval between regularly occurring ectopic beats, from Lead V_2 to Lead V_5. The same interval is observed between Lead V_3 and Lead V_6.

Because of the suspected rheumatic infection, she was transferred to the House of the Good Samaritan for fur-

ther study. After 2 months' stay there, her cardiac condition was definitely pronounced not rheumatic, and the murmur was thought to be possibly of "functional" or congenital origin.

It was not until her final admission to the Children's Hospital at the age of 10 years, in January, 1949, that her condition was definitely labeled as Friedreich's disease. She was then transferred to the Massachusetts Hospital School at Canton, Massachusetts, where the physical signs were the same as at the Children's Hospital. X-ray films of the heart again revealed cardiac enlargement, involving mainly the left ventricle. Electrocardiograms (Fig. 7) showed an inverted T wave in Leads 2 and 3 and in Lead aVF and the chest leads, with tall R waves in Leads V_5 and inverted T waves in Leads V_5 and V_6.

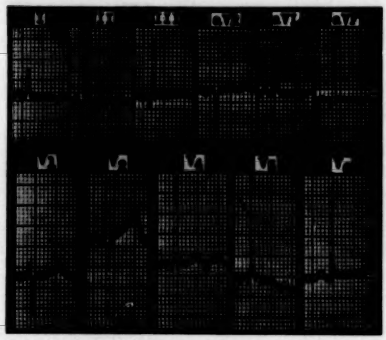

FIGURE 5. *Electrocardiogram in Case 3, Showing Inverted T Wave in Lead 1, Diphasic T Wave in Lead 2 and Tall R Wave in Lead aVF, with Diphasic T Wave, and Inverted Wave in Leads V_4 to V_6.*

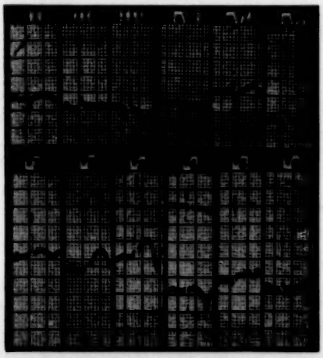

FIGURE 6. *Electrocardiogram in Case 4, Showing Inverted T Waves in Leads 1 and 2, and Tall R Wave in Lead aVF, with Inverted T Wave in Leads V_1 to V_5, with Diphasic T Wave in Lead V_6.*

Her course at the Massachusetts Hospital School has been one of progressive weakness and ataxia, with no circulatory symptoms.

CASE 6. D. R., a 9-year-old boy, was first admitted to the Children's Hospital in January, 1947, at the age of 5½ years with the chief complaint of ataxia of 1 year's duration. The family history revealed one sibling with Friedreich's disease. Physical examination showed marked ataxia, a positive Romberg sign, absent deep tendon reflexes, bilateral cavus deformity of the foot and scanning speech. Cardiac examination was negative.

In March, 1947, he was transferred to the Massachusetts Hospital School, where the physical examination was the same as the one described above. X-ray films of the heart revealed no abnormalities. An electrocardiogram (Fig. 8)

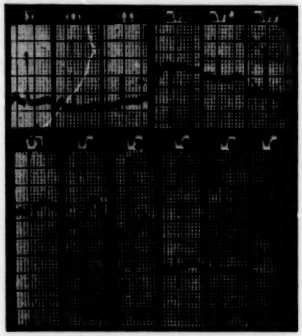

FIGURE 7. *Electrocardiogram in Case 5, Showing Inverted T Waves in Leads 2 and 3 and Inverted T Wave in Lead aVF and Chest Leads, with Tall R Wave and Inverted T Waves in Leads V_5 and V_6.*

disclosed inverted T waves in Leads 1 to 3, and an inverted T wave in Lead aVF. The chest leads showed uniformly inverted T waves with tall R waves in Leads V_4 to V_6.

DISCUSSION

Friedreich, in his original description in 1863, described 6 cases of ataxia, 5 of which showed clinically noticeable cardiac abnormalities. Autopsy was performed in 3 of them, and 2 of these showed "myocardial damage." In 1887, Pitt[3] was the first to emphasize the cardiac manifestations associated with this disease. Post-mortem examination of his case disclosed diffuse myocardial fibrosis. In 1946, Dorothy Russell[4] reviewed 4 autopsied cases. All of them revealed extensive myocardial fibrosis and fatty degeneration, as well as coronary sclerosis without obstruction. She proposed the theory that "toxins" are probably the underlying etiologic factor in both the cardiac and the neurologic manifestations. Others favor the concept that the cardiac manifestations are caused by

lesions of the nervous system. As evidence for this, Piron[5] presented the case of a twenty-two-year old man who developed a fatal attack of angina pectoris after a skiing injury that damaged the dorsal spine. The similarity of the cardiac manifestations and nervous-system lesions in this case to those observed in Friedreich's disease led Piron to consider the cardiac involvement in the latter an additional manifestation of the neurologic damage.

A number of reports from the clinical and electrocardiographic viewpoints have appeared in the literature.[6-15] Several of them described heart murmurs, cardiac enlargement, disturbances in rhythm and even congestive failure. The most extensive review of the electrocardiographic changes is that of Evans and Wright,[15] who described 28 patients with Friedreich's ataxia. Twelve of these showed definite and significant abnormalities in the electrocardiogram. These consisted mainly of negative T waves of coronary-type in either Lead 1 or Lead 3, low voltage of the T waves, or bundle-branch block. Another 10 patients in this series showed minor abnormalities with deep and slurred S waves. In addition, these authors noted that affected members of the same family tended to show identical electrocardiographic changes. They believed, therefore, that the electrocardiogram may help to establish the diagnosis of Friedreich's disease when the neurologic manifestations are not altogether typical of the condition. While a normal tracing does not exclude diagnosis of the disease, an abnormal record lends valuable support to the diagnosis. Finally, they noted that the more serious examples of Friedreich's disease are more likely to show cardiac involvement.

The salient points of the past history and the cardiac findings of our 6 cases are summarized in Table 1.

Four of our patients were men; 2 were women. A positive family history could be elicited in 2 patients. The age at onset was two to seven years. The initial diagnosis was not Friedreich's disease in 3 out of these 6 patients. Cerebellar tumor was suspected in 2, and chorea and glycogen-storage disease in 1 each.

Only 1 of our patients had any symptoms directly referable to the circulatory system: Case 2 was admitted with signs of cardiac failure, and later developed chest pains suggestive of angina pectoris.

Irregular rhythm was noted in 2 of our patients. Cardiac enlargement was seen in the x-ray films in 3 cases. All but 1 patient showed a heart murmur. Electrocardiographic tracings were available in 5 patients; they were all abnormal.

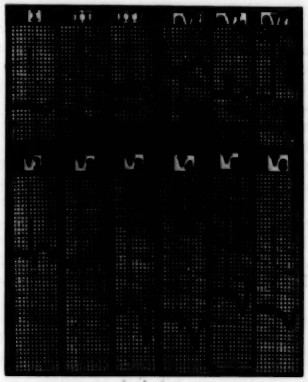

FIGURE 8. *Electrocardiogram in Case 6, Showing Inverted T Waves in Leads 1 and 3 and Tall R Wave with Inverted T Wave in Lead aVF, and Chest Leads with Inverted T Waves in Leads V_2 to V_6.*

Most of these observations are in agreement with those mentioned in the literature. We have not found, however, any previous mention of pericardial effusion in a case of Friedreich's disease, as seen in Case 2. Nor are we aware of an instance of the ventricular type of parasystole as shown in the tracing of this same patient. This electrocardiographic diagnosis is borne out by the fact that the

TABLE 1. *Salient Points of History and Cardiac Examination in 6 Cases.*

Case No.	Sex	Family History	Age at Onset of Ataxia	Initial Diagnosis	Cardiac Symptoms	Rhythm	Cardiac Signs		Electrocardiographic Changes
							Enlargement	Murmur	
			yr.						
1	M	Negative	4	Friedreich's disease	None	Regular	+	+	No tracing
2	M	Negative	3½	Van Gierke's disease	Congestive failure; pain.	Irregular	+	+	+
3	F	Negative	7	Cerebellar tumor	None	Regular	0	+	+
4	M	Positive	2	Friedreich's disease	None	Regular	0	+	+
5	F	Negative	4½	Cerebellar tumor and chorea, with rheumatic heart disease	None	Irregular	+	+	+
6	M	Positive	4	Friedreich's disease	None	Regular	0	0	+

ectopic ventricular complexes had the same configuration whenever they occurred, and by the fact that they had a characteristic rhythm, distinctly different from that of the basic sinus mechanism. In cases in which the ectopic ventricular complex did not occur, the long interval between the last and the next ectopic complex is an exact multiple of the short interval between regularly occurring ectopic beats. This finding establishes the existence of a parasystolic focus.[16] It must be mentioned that such a diagnosis can be made only on the strength of a long tracing.

In addition to these two previously unreported phenomena in Friedreich's disease, we can report the electrocardiographic phenomena in more detail than has been done in previous publications. None of the cardiograms in these cases included unipolar limb or chest leads. All our tracings contain these leads. The pattern uniformly shows inverted T waves in the complexes representing left ventricular potentials — that is, aVF (in vertical hearts) and Leads V_5 and V_6. Some of the chest leads show inverted T waves in Leads V_1 through V_4 as well. These, however, may occur normally in children. The inverted T waves in Leads V_5 and V_6 are, on the other hand, completely abnormal. These cardiographic patterns typical of coronary-artery disease suggest ischemia in the left ventricle.

On the basis of the autopsy findings of Case 1, the anginal type of pain in Case 2 and electrocardiograms indicative of coronary-artery disease in every case studied, it seems not too far-fetched to assume that involvement of the coronary arteries of the left ventricle may play a decisive role in the production of the myocardial fibrosis.

We have no explanation of the etiology of this arterial change. One may speculate whether biopsy of skeletal muscle in Friedreich's disease might show similar vascular changes, thus explaining the profound weakness and wasting that characterize this condition.

We have no conclusive figures concerning the frequency with which electrocardiographic changes are observed in Friedreich's disease. Evans and Wright, in the largest series published, estimate it at about 30 per cent. The electrocardiogram may thus be a very useful procedure in cases in which the chief complaint is inco-ordination, since it tends to differentiate patients with Friedreich's disease and those suffering from other types of ataxia. A normal electrocardiogram obviously does not exclude Friedreich's disease, but an abnormal one may well establish the diagnosis.

Summary

Six cases of Friedreich's ataxia with associated cardiac manifestations are reported. Post-mortem studies in 1 revealed diffuse myocardial fibrosis and extensive coronary-artery obstruction, chiefly in the left ventricle. Pericardial effusion and the ventricular type of parasystole, two heretofore unreported findings in this disease, were found in another patient. Five patients showed electrocardiographic patterns indicative of coronary-artery disease involving the left ventricle.

The theory is advanced that coronary-artery disease may be the etiologic factor in the myocardial damage found in these cases.

In view of the sometimes difficult diagnostic problem presented by these patients, it is suggested that the electrocardiogram be included as a standard diagnostic tool in cases of Friedreich's ataxia.

We are indebted to Dr. Bronson Crothers for bringing to our attention these interesting cases; and to Dr. Sidney Farber for his kindness in furnishing the pathological data for the first case, including the illustrations for Figures 1 and 2.

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EXTREME HYPERGLOBULINEMIA IN SUBACUTE HEPATIC NECROSIS*

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SERUM protein disturbance has been recognized in liver disease since Jolles,[1] in 1902, first described depression of the whole-blood proteins in cirrhosis. Several years later, Gilbert and Chiray[2] and Grenet[3] observed this to be due to serum protein depression. In 1925 Filinski[4] showed that the serum protein abnormality in cirrhosis included not only albumin depression but also globulin elevation. Subsequent observations[5-31] have shown these findings to be so common in intrinsic liver disease that the opinion has been advanced[12, 22] that the diagnosis of cirrhosis should be held in doubt in the absence of serum globulin elevation. While for prognostic value greater stress has been laid on the serum albumin level,[16] extreme hyperglobulinemia is also associated with a poor prognosis.[19-22] In spite of the frequency of hyperglobulinemia in cirrhosis, the levels attained are usually moderate (3 to 6 gm. per 100 cc.), and it is rare indeed for globulin levels to become elevated to the extent noted in multiple myeloma, lymphogranuloma venereum, sarcoidosis, and certain chronic infections. Whenever extreme hyperglobulinemia has been described in liver disease, it has been associated with subacute hepatic necrosis or postnecrotic cirrhosis, on a presumed infectious or toxic basis.[19-22] Whereas no case of Laënnec's cirrhosis has been observed with serum globulin values above 6.12 gm. per 100 cc., 4 patients with postnecrotic cirrhosis have been described, in addition to the case presented below, as having total protein values above 11 gm. per 100 cc. or a globulin value above 8 gm. per 100 cc. or both.[19, 20, 22, 23] As shown in Table 1, the prognosis is grave for patients who have intrinsic liver disease with this degree of hyperglobulinemia.

While none of these reports of massive hyperglobulinemia have presented electrophoretic studies, in the available electrophoretic analyses[24-31] of cases of Laënnec's cirrhosis and of hepatitis (both acute and chronic), the most marked abnormality in the globulin fraction has been in the gamma globulin component. The highest value of gamma globulin previously reported was 4.4 per cent of the total protein, or a value of approximately 4 gm.[25] The following case of subacute hepatic necrosis is, to our knowledge, the only example of hyperglobulinemia of this degree in hepatic disease that has been subjected to electrophoretic study, and also shows the highest gamma globulin yet reported in liver disease.

TABLE 1. *Massive Hyperglobulinemia in Liver Disease.*

AUTHOR	DIAGNOSIS	HIGHEST TOTAL PROTEIN gm./100 cc.	HIGHEST GLOBULIN gm./100 cc.	OUTCOME
Cameron and White[19]	Subacute yellow atrophy	10.00	8.00	Death
Cabot Case[20]	Post-atrophic cirrhosis	12.01	9.94	Death (43 months)
Bjørneboe[21]	Subchronic hepatitis	11.67	9.67	Death (12 months)
	Subchronic hepatitis	11.06	8.16	Presumed recovery
		12.29	9.84	Presumed recovery
Zimmerman, Heller and Hill (present study)	Subacute hepatic necrosis	11.20	9.90	Death (8 months)

CASE REPORT

W. J. M., a 36-year-old executive in a government agency, was admitted on February 21, 1949, because of jaundice of 3 weeks' duration. Six months earlier, 3 small reddish "patches" had appeared on the chest. Three weeks before admission, a yellow tinge was noted in the eyeballs and skin. Except for the presence of this jaundice, he was completely asymptomatic. He specifically said that he had no nausea, vomiting, abdominal pain, fever, or discomfort during the present illness or in the recent past. There was no history of injections of any sort or of the withdrawing of blood samples at any time during the previous year. One of his children had had a febrile illness (diagnosed by clinical and laboratory examination as infectious mononucleosis) several weeks before the patient developed jaundice, but he had not been aware of any exposure to other infectious diseases. Likewise, exposure to hepatotoxic agents of all varieties, carefully and completely enumerated, was denied. The patient, a man of considerable intelligence, continued to examine his immediate and remote past for such exposure. The past medical history was completely uneventful, and shed no light on the present illness.

Physical examination showed a well developed, well nourished, vigorous-appearing man, moderately jaundiced. The skin of the anterior portion of the chest was completely hairless. There were three small spider angiomas on the anterior upper portion of the chest, and one large spider nevus on the nape of the neck. No palmar erythema was present. A soft, rounded, slightly tender liver edge was felt 3 cm. below the right costal margin at the midclavicular line. The spleen was firm and palpable just below the left costal margin. There were no enlarged cervical, axillary or epitrochlear lymph nodes.

Laboratory data are shown in Table 2. Attention should be paid to the height of the icterus, the extreme hyperglobulin-

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emia, and the definite hypocholesterolemia, as well as to the other pertinent data. Electrophoretic patterns of the serum are shown in Figure 1, and the values in Table 3. The elevation of globulin was due almost entirely to the gamma globulin level of 7.31 gm. per 100 cc.

Five days after admission to the hospital, a needle biopsy of the liver was performed (Fig. 2*A*). This revealed distortion of the liver architecture and increased fibrosis around the lobules, associated with a proliferation of some of the bile ducts. At the periphery of the lobules, newly formed fibrous tissue containing many inflammatory cells, largely lymphocytes, was noted. The liver cells were large and granular, and some of the individual cells showed necrosis. Increased bile pigment was found in the more peripherally located cells. Two weeks later the needle biopsy was repeated, revealing a picture generally similar to the previous one. There was an absence of fatty metamorphosis in both specimens. At this time a tentative diagnosis of postnecrotic scarring was made, with the recognition that active necrosis was continuing.

Bone-marrow aspiration showed 11 per cent plasma cells, some in clumps of 5 or 6, but no typical myeloma cells. This was interpreted as consistent with the hyperglobulinemia.

Treatment consisted of complete bed rest and a high-calorie, high-protein diet, with supplements of multivitamins and a vitamin B group concentrate, as well as 2 gm. of methionine daily, taken orally. Throughout the following 8 weeks, the patient's symptoms did not change materially. His appetite, morale and weight were preserved. Shortly after admission, fetor hepaticus was noted, which varied in intensity from day to day, but there was no parallel fluctuation of the subjective part of the illness. The patient was allowed to go home on March 29, but remained on a regimen identical with that in the hospital. At home, he felt well until April 22, when he complained of chilliness and a rise of temperature to 101°F. The fever lasted only 1 day, but thereafter he complained of drowsiness, and the jaundice became more pronounced. His appetite remained good. He was returned to the hospital on April 27, when the fetor hepaticus seemed deeper, and several more spider angiomas were visible. During the next 2 days, increasing drowsiness developed, followed by several episodes of maniacal behavior, and, on the 4th day, deep coma. On that day the temperature rose to 104°F. He developed signs of bilateral lower-lobe pneumonia, and died that evening. Treatment during the last 4 days of life included plasma and glucose given intravenously.

TABLE 2. *Laboratory Data During Course of Subacute Hepatic Necrosis.*

WEEK OF DISEASE	HEMOGLOBIN	HEMATOCRIT	WHITE-CELL COUNT	NEUTROPHILS	LYMPHOCYTES	EOSINOPHILS	MONOCYTES	ALBUMIN	BENCE-JONES PROTEIN	SUGAR	BILE	UROBILINOGEN	THYMOL TURBIDITY	CEPHALIN FLOCCULATION
	gm./100 cc.	%	x10³	%	%	%	%						units/100 cc.	
3	11.1	35	7.35	78	21	1	—	Trace	0	0	Positive	1-40	23.0	++++
5	11.1	34	9.45	71	28	1	—	0	0	0	Positive	1-80	14.0	++++
7	10.7	34	6.75	64	22	12	2	0	0	0	Positive	1-40	16.0	++++
11	10.5	34	8.35	72	25	3	—	Trace	0	0	Positive	—	13.5	++++

*Plasma dilution.

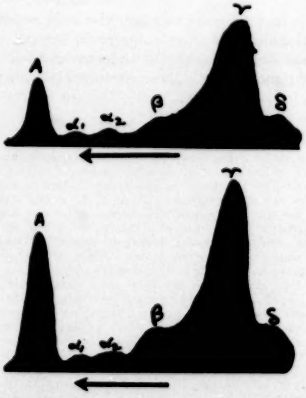

FIGURE 1. *Electrophoretic Patterns of Serum (Courtesy of Dr. Gerson Kegeles, National Cancer Institute, Bethesda, Maryland). 1 vol. of serum plus 2 vol. of buffer, two hours and fifty-five minutes at 6.38 volts per centimeter (buffer — N Na-diethyl barbiturate —0.02 N diethyl barbituric acid, at a pH of 8.57).*

At autopsy there was 500 cc. of clear, bile-tinged fluid in the abdomen. The liver weighed 1440 gm. Its consistence was increased, and the cut surface was coarsely and irregularly nodular. The nodules were sharply circumscribed, measured less than 1 cm. in diameter and varied from green to yellow. The fibrous markings were considerably more prominent than usual. On microscopical examination, the normal lobular architecture was almost completely destroyed. The parenchymal cells were arranged in nodules of varying size, separated for the most part by fairly wide fibrous bands containing a heavy infiltration of lymphocytes and plasma cells. In some places a few residual liver cells were found near the centers of the lobules (Fig. 2*B*); elsewhere, the cells had completely disappeared, and the lobules were outlined only by proliferating bile ducts at their peripheries (Fig. 2*C*). Still other foci revealed nodules of regenerated hepatic cells without significant necrosis (Fig. 2*D*). Bile-duct proliferation was found in varying degrees throughout. Many of the bile canaliculi contained bile thrombi. An occasional cell revealed a small cytoplasmic vacuole. The anatomic diagnosis was subacute hepatic necrosis with cirrhosis.

DISCUSSION

This case is primarily of interest because of the marked hyperglobulinemia, which was due almost exclusively to gamma-globulin increase, illustrating the association of this feature with subacute hepatic necrosis. There are several possible causes of hyperglobulinemia in liver disease. It has been suggested that the globulin level rises in compensation as the albumin level falls.[20, 22, 26] On the other hand, it may be that the globulin rises as a

specific result of liver injury in hepatitis, and that the damaged liver is also unable to form albumin.[26] Most observers agree, however, that the greater the disturbance in serum proteins considered from the standpoint of either albumin depression or globulin elevation, the more severe the cirrhosis.

In infectious and toxic hepatitis, an increase in serum globulin, albeit usually of small degree, is a frequent finding.[24-26] Furthermore, it has been shown that this elevation is largely, although not exclusively, in the gamma globulin fraction.[24-26, 22] This may represent the reaction of the liver injury in a nonspecific fashion, or it may, as in other infectious diseases, represent the formation of antibodies,[9, 20, 24, 25] which are known to be present in the gamma globulin fraction.[20] Studies of antibody formation in hepatitis led Eaton, Murphy and Hanford[24] to suggest that autoimmunization may occur. They thought that this was the mechanism for the continued activity in chronic hepatitis and for the progressive necrosis in subacute yellow atrophy. According to this concept, the initial injury causes an alteration in liver protein, which stimulates the formation of anti-liver antibodies. These newly formed antibodies produce more liver injury, thus releasing more altered liver protein, which again contributes to the vicious circle of continuing necrosis. This theory is commendable as an explanation of both the necrosis and the mounting of the gamma globulin level with the progress of the disease. In terms of this theory, extreme hyperglobulinemia may be expected in cases in which active necrosis is occurring at a merely moderate pace. In massive hepatic necrosis — or acute yellow atrophy, as it is also called — death probably occurs too quickly to permit the development of a high level of antibodies, and therefore of a significant hypergammaglobulinemia. In the unusual trophopathic hepatitis — that is, the cirrhosis following fatty infiltration (the "alcoholic" liver) — death of cells is a process of necrobiosis. The amount of antigenic liver protein thus released is probably too small to stimulate the degree of gamma globulin change that occurs with more massive but not immediately lethal necrosis (subacute yellow atrophy, subacute hepatic necrosis and chronic hepatitis).

It has been suggested that gamma globulin comes from the cells of the reticuloendothelial system,[35] lymphocytes[36] or plasma cells.[37, 38] While some experimental evidence has been presented for each of these theories, a clinical correlation between plasma cells and serum globulin has been noted.[39, 40] In recent years it has been emphasized that patients with hyperglobulinemia frequently have increased plasma cells in the bone marrow as well as in the tissues.[40, 41, 42] This, however, has been disputed as a constant finding.[42] It is of interest that, in the case reported above, increased plasma cells in the bone and marrow and liver were noted.

The etiology of this case remains obscure. It seems clear from the histologic findings that it represents an active hepatitis. The history offers no positive indications of a potentially responsible

TABLE 2 (*Concluded*).

Week of Disease	Alkaline Phosphatase	Cholesterol		Icteric Index	Serum Protein			Non-protein Nitrogen	Sedimentation Rate	Prothrombin*	Blood Kahn Test	Heterophil Agglutination	Frei Skin Test	Chest Film
		Total	Esters		Total	Albumin	Globulin							
	units/100 cc.	mg./100 cc.	mg./100 cc.		gm./100 cc.	gm./100 cc.	gm./100 cc.	mg./100 cc.		%				
3	7.4	121	27	50	10.2	1.9	8.3	—	32	44	Negative	Negative	Negative	Normal
5	—	96	22	55	11.7	2.2	9.5	—	—	28	—	—	—	—
7	—	120	33	54	9.6	1.4	8.2	34	—	—	—	—	—	—
11	5.4	—	—	85	11.2	1.3	9.9	24	—	27	—	—	—	—

TABLE 3. *Electrophoretic Analyses of Serum Proteins.*

Week of Disease	Albumin Concentration		Alpha1 Globulin Concentration		Alpha2 Globulin Concentration		Beta Globulin Concentration		Gamma Globulin Concentration		Total
	Relative	Absolute	Relative	Absolute	Relative	Absolute	Relative	Absolute	Relative	Absolute	
	%	gm./100 cc.	%	gm./100 cc.	%	gm./100 cc.	%	gm./100 cc.	%	gm./100 cc.	gm./100 cc.
3	15.3	1.57	2.4	0.25	3.9	0.41	7.3	0.75	71.1	7.31	10.29
7	19.7	1.70	2.7	0.20	3.1	0.27	9.0	0.78	65.9	5.69	8.64

toxic agent. This patient was a highly intelligent man, who tried conscientiously to recall significant exposure to toxic agents of any sort. His consumption of alcohol was definitely moderate. Furthermore, the pathological examinations of the liver, both gross and microscopical, satisfy the criteria of postnecrotic cirrhosis or subacute hepatic necrosis[42] — not those of "alcoholic" cirrhosis.[42, 44] Quite conceivably, this could represent an especially severe form of hepatitis, presumably infectious, similar in its course to the epidemic recently described in Denmark.[21] It is, however, impossible to prove this contention — and in the absence of epidemiologic confirmation and of a significantly typical onset, this hepatitis must be considered idiopathic. An attempt to associate the fatal illness of this patient with the infectious mononucleosis in his child would be sheer speculation, in the pres-

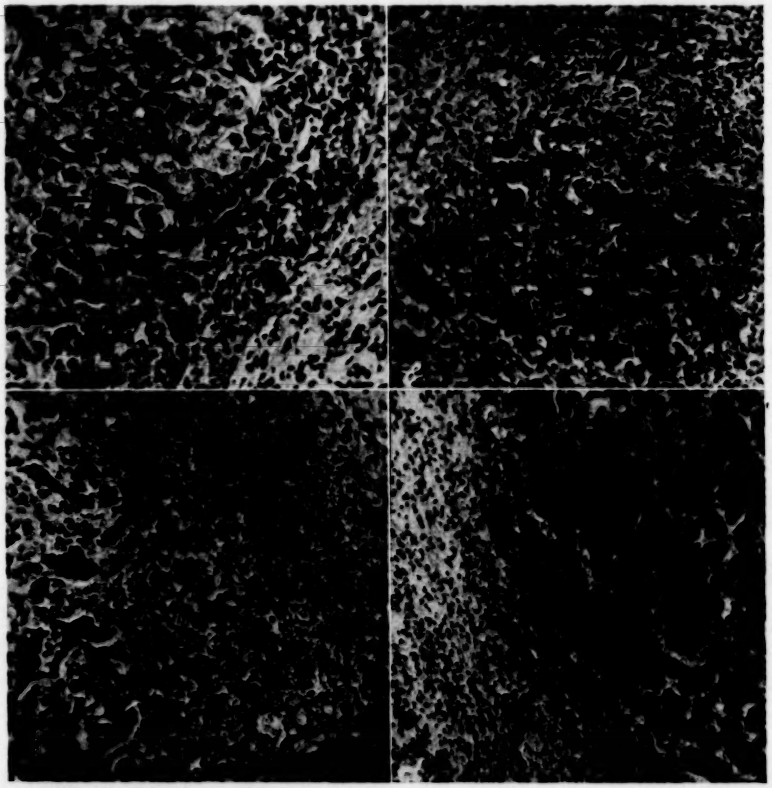

FIGURE 2. *Photomicrographs of Sections of the Liver.*

A = *needle biopsy. A regenerating lobule with an inflammatory cell infiltration is still evident at the periphery. A band of condensed fibrous tissue surrounds the lobule. At autopsy a few residual liver cells* (B) *are seen near the center of lobule.* C = *proliferating bile ducts at the periphery of a lobule in which all parenchymal cells have disappeared.* D = *a regenerated lobule with loosely arranged cords of liver cells* (*it is surrounded by a broad band of fibrous tissue containing numerous inflammatory cells*).

ence of a negative heterophil-antibody agglutination and the absence of hematologic and clinical features characteristic of that disease.

The waxing and waning of the fetor hepaticus, vascular angiomas and icterus are evidence that this patient's course was not consistently downhill. Nevertheless, it was irreversible and led to an early death. It is of interest to emphasize the paucity of subjective symptoms in the course of severe and ultimately lethal hepatic disease.

Summary

A case of massive hyperglobulinemia in a patient with subacute hepatic necrosis is described, and the electrophoretic pattern presented. This case shows one of the five highest globulin values, and the highest gamma globulin level, yet reported in liver disease. Evidence from the literature is cited to show that extreme hyperglobulinemia in liver disease is apparently restricted to postnecrotic cirrhosis and does not occur to the same degree in Laënnec's cirrhosis. It is suggested that marked hyperglobulinemia, when it occurs, represents a mounting production of anti-liver protein antibody that continues to cause necrosis of the liver. Judging by the few cases in which it has been seen, extreme hyperglobulinemia in liver disease seems to be a grave prognostic sign.

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DIAGNOSTIC AND THERAPEUTIC PROBLEMS IN BENIGN MEDIASTINAL TUMORS*

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RAPID developments in thoracic surgery and increased use of mass roentgen surveys during the past decade have revealed a greater incidence of mediastinal lesions than heretofore suspected, have shown the necessity of efforts at more careful and exact diagnoses, and have brought about a profound change in the general attitude toward their treatment.

For the numerous benign lesions which occur in the mediastinum, various classifications have been employed. All discrete and well circumscribed lesions have by usage been classified as benign tumors, although various types of cysts encountered are, in the strictest sense, not true neoplasms. In general, mediastinal tumefactions may arise as congenital malformations, as the result of infection or degenerative change or as true neoplasms. These lesions may also be catalogued topographically, according to the frequency of their occurrence in the various mediastinal compartments.

Any account of a clinical experience with benign intrathoracic and mediastinal tumors would be incomplete without reference to those lesions that simulate tumor and cause confusion in differential diagnosis. We refer particularly to lesions that arise outside the thoracic cavity and subsequently intrude by one route or another in such a fashion as to simulate strongly a benign encapsulated mediastinal tumor. Among these are:

1. *From the cervical region*, thyroid adenomata. These may be classified as (a) substernal extensions from one or the other thyroid lobe (usually lower pole), and (b) truly aberrant thyroid tissue. The first group are relatively common, especially in endemic goiter areas, but the latter, as pointed out by Rives,[1] are much rarer. There have been 2 such aberrant cases in our own clinical experience. The first, a fifty-six-year-old man, who had undergone a cervical thyroid adenomectomy in another hospital twenty years previously, had a discrete lesion of the right superior mediastinum in the retrotracheal position, which caused pressure manifestations. The second case, that of a sixty-six-year-old woman, revealed bilateral adenomata in the neck, and a massive unattached mass in the deep posterior mediastinum. The latter is our only case among 12 mediastinal goiters that required thoracotomy for its removal, cervical and thoracic approaches being used successively in the course of the same operative intervention.

Roentgenologically, the substernal extensions of thyroid origin are easy to recognize. There is usually some degree of tracheal deviation and compression, as well as a homogeneous density continuous through the superior thoracic inlet, with a cervical shadow. Palpable enlargement of the cervical thyroid gland is usually found, but not always. A tracer dose of radioactive iodine given in doses of 100 microcuries by mouth may be helpful in differential diagnosis when followed by topographical Geiger counts in twenty-four hours. As pointed out by Sweet[2] in a recent publication, substernal goiters do not invariably occupy a pretracheal position. In our experience with twelve cases, six were retrotracheal or retroesophageal. Our radiologists have long since learned not to rely on the antetracheal position as a diagnostic criterion for intrathoracic goiter.

2. *From the bony thorax*, chondroma or chondrosarcoma may grow internally with little or no discernible change in rib detail, and no externally visible or palpable tumor or deformity. These chondrosarcomas may be discrete, homogeneous in density and usually in the posterior position. However, Edwards[3] has reported a large one arising from the lateral chest wall. Ewing's sarcoma arising in the rib may develop large intrathoracic extensions, which in one instance (a nine-year-old girl) simulated a tumor of the left upper lobe.

3. *From below the diaphragm*, herniation through congenital or acquired defects of the various foramina may resemble tumor. This is particularly true of the Morgagni type, located anteriorly and parasternally, especially when the sac contains nothing but omental fat. Duodenal and jejunal diverticula, though exceedingly rare, may also enter the posterior mediastinum through the diaphragm, as recently described by Gross.[4]

4. *From the heart or large vessels*, aneurysmal dilatations. In these cases, other evidences of arteriosclerosis or syphilis (by history or on careful physical examination), and the findings on roentgenoscopy, laminagraphy, kymography, and arteriography may all be helpful in diagnosis. We have had some success with diagnostic pneumothorax and thoracoscopy in this group, but occasionally an exploratory thoracotomy is necessary to make an absolute diagnosis.

5. *From the spinal cord*, meningoceles have been reported.[5] We have had no experience with this group.

As previously mentioned, position of the lesions in the various mediastinal compartments is a great

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aid in diagnosis. While dermoid tumors are typically located anteriorly to the midline, they may on rare occasions exist posteriorly. This is illustrated by one of our cases, a newborn boy operated upon at the age of fifteen days because of pressure manifestations.

Bronchogenic cysts are characterized by a lining of epithelium of the respiratory tract and the variable presence of other bronchial elements in the wall. They may occur anywhere in the upper paratracheal region, along the primary or secondary bronchi, and even in aberrant positions (such as on the diaphragm), quite separate from the lung. In 3 of our cases, histologically characteristic bronchogenic cysts arose in the esophageal wall, intimately attached to the mucosa and displacing thinned-out esophageal musculature over them. Care should be taken, in excising these lesions, not to open the esophageal lumen during the dissection. Leiomyomata of the esophagus may be quite bulky, simulating mediastinal tumor; this is one reason for employing a barium swallow in the roentgenologic diagnosis of these cases when the tumor is posteriorly situated.

Tumors of neurogenic origin are usually posterior and paravertebral. Enlargement of an intervertebral foramen may sometimes be demonstrated radiologically, and signs of cord compression may exist, on rare occasions. Such combined spinal and intrathoracic lesions ("dumbbell tumors") may be lipoma, neurofibroma or sarcoma. In 3 cases of ganglioneuroma surgically removed in this clinic, the tumors were of considerable size, and lay along the sympathetic chain, as shown by operative dissection and by demonstration of sweating and skin resistance changes in the corresponding upper extremity after extirpation of the tumor. It is of considerable diagnostic interest that all three of these cases showed macroscopic or microscopic calcification; in two the calcium was distinctly visible in roentgenographic studies. In one case of cervical ganglioneuroma removed from the left cervical sympathetic chain of a five-year-old boy, a fatal malignant mediastinal sympathicoblastoma made its presence manifest by serosanguineous pleural effusion six years later.

The anterior cardiophrenic angle is frequently the site of mediastinal lesions that present a particularly challenging diagnostic problem. These include pericardiocelomic cysts, cystic lymphangioma, dermoid cysts, partial eventration of the diaphragm, and Morgagni hernia. The latter do not always contain gas-filled viscera, or such a condition may be obscured by folds of omentum. A barium enema studied in posteroanterior and lateral projections (or a lateral plain film in the erect position) may demonstrate an abnormally high right colon and hepatic flexure. Diagnostic pneumothorax may be quite helpful in differentiating tumefactions from the lung or diaphragm, or both, but adhesions can nullify its effectiveness. A proper preoperative differential diagnosis is important here, because a Morgagni hernia is certainly better treated by laparotomy than by thoracotomy, a conclusion reached after some experience with both methods.

Cystic (especially multiloculated) tumors of the parasternal cardiophrenic angle may on careful histologic study show minor lymphatic channels, smooth muscle and elastic tissue, thus proving their origin from anterior lymphatic trunks rather than from pericardial anlage. They may be very large, plastic in outline, and closely simulating a high or eventrated diaphragm. Right-sided diaphragmatic hernia with the liver displaced into the chest may also resemble a thoracic tumor, but the elevation of the inferior liver border above the normal position is a diagnostic aid in this instance. This was seen in a recent case, that of an 8-year-old boy, whose liver lay mostly in the right chest through a congenital Bochdalek hernial defect.

There has been a tendency to regard any lesion of the mediastinum that is discrete, cystic and containing sterile gray putty-like material as a degenerated caseous tuberculous focus ("tuberculoma").[6] Histologic study of such lesions in the anterior parapericardial position may reveal thymic elements in the wall of the cyst. This was demonstrated in a tumor removed from the left pericardial position in a fifty-seven-year-old woman, who complained only of vague weakness and fatiguability. A large major cyst contained sterile putty-like necrotic debris superficially resembling a tuberculoma, while several smaller cysts showed crystal-clear fluid and their walls revealed Hassall's corpuscles in various stages of cystic degeneration. The diagnosis was thymic cystadenoma.

"Tuberculomas," usually in involved hilar nodes, are found without clinically recognizable pulmonary involvement, and may cause confusion in diagnosis. A very recent case in a thirty-two-year-old man presented an asymptomatic lesion roentgenologically identical with a bronchogenic cyst.

Echinococcal cyst of the mediastinum is known to exist; however, it is much more common in the liver and lung. Evidence of cysts elsewhere, a history of exposure in an endemic area and the Casoni skin test will usually clarify the diagnosis.

Indications for Surgery

The indication for surgical excision of a presumptively benign mediastinal tumor rests on the demonstration of its existence. Whereas many are asymptomatic and remain so for many years, others increase appreciably in size, and cause pressure manifestations in the bronchial tree, esophagus or large vessels. Severe pain is not a common manifestation, and is usually associated with the neurogenic group of tumors. However, a completely satisfactory differential diagnosis cannot be made without surgical excision and pathological study;

this is the chief reason for recommending surgery in all cases. In the past few months we explored a presumptively benign lymphatogenous cyst above the right diaphragm, only to find a fibrosarcoma that was not completely resectable.

The operative mortality risk of these resections for benign lesions is extremely low. In our series of benign tumors, there was 1 hospital death in 31 cases. This was an obese 71-year-old woman, an arteriosclerotic cardiac patient with a very large anterior paracardial thymic tumor. She was not myasthenic, but she died suddenly on the ninth day after an apparently successful resection.

TABLE 1. *Types of Benign Primary Mediastinal Tumors.*

TYPE OF TUMOR	NO. OF CASES
Bronchogenic cyst (of esophagus in 3 cases)	7
Pericardiodiaphragmatic cyst	4
Dermoid cyst	4
Neurofibroma	4
Ganglioneuroma	3
Tumor of aberrant thyroid gland	2
Embryoma, pulmonary	2
Lymphangioma, cystic	2
Thoracic-duct cyst	1
Thymus, cystadenoma	1
thymoma	1
Total	31

The anesthesia used in our cases has always been general, and usually endotracheal. The operative approach has varied with the location of the lesion. For some anterior tumors, a submammary approach with intercostal incision has been successfully employed, and gives an excellent cosmetic result in the female. The most useful incision, and the safest for exposure in unexpectedly difficult cases, is the long posterolateral thoracotomy with or without rib resection. This allows freedom of action and adequacy of exposure, making for better hemostasis, easier operating, and safety for the patient.

A list of the mediastinal tumors diagnosed and treated in this service between 1942 and 1949 is presented in Table 1.

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HOSPITAL OUTBREAK OF INFECTIONS WITH *SALMONELLA NEWINGTON**

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BOSTON

CASES of infection with *Salmonella newington* were found with unusual frequency at the Boston City Hospital during the latter part of 1949 and early in 1950. A survey of the records of the bacteriological laboratory of this hospital¶ revealed that strains of this type of salmonella had been isolated from 57 persons during the eighteen-month period between November, 1948, and April, 1950, but had not previously been encountered for several years. In view of the relative infrequency of infections in man with *S. newington*,[1,2] and because the cases from which the strains were isolated were found over so long a period, the records of the patients involved were reviewed, and a brief, though incomplete, survey of food handlers was made at the hospital in an effort to find possible sources of these infections. This communication contains a brief summary of the clinical and epidemiologic features of the cases and of the attempts made to discover carriers among the food handlers.

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¶We are indebted to Miss Marion E. Lamb and Miss A. Kathleen Daly of the Bacteriological Laboratory, Mallory Institute of Pathology, for isolating and identifying the strains, for submitting them to the salmonella center for classification, and for assistance in the collection of the bacteriological data. The salmonella typings were carried out in the laboratories of Dr. E. Seligmann.

EPIDEMIOLOGIC ASPECTS

The 57 patients from whom *S. newington* was isolated included 34 males and 23 females. They ranged in age from two to eighty-two years; 72 per cent were under thirty or over sixty years old. There were 13 children who either attended school or were of preschool age. Hospital employees among the patients included 7 physicians and 4 nurses. The adult female patients were mostly housewives, and the occupational histories of the remaining patients were not relevant.

Only 22 of the 55 patients for whom adequate data are available‖ first presented themselves with acute gastrointestinal symptoms, which included diarrhea or nausea and vomiting, or all three,

‖The records of 2 patients were not available, and the data in their cases are incomplete.

and which could therefore be interpreted as caused by salmonella infection. Four additional patients were under study for chronic gastrointestinal disease (one each for diverticulitis, cancer of the rectum, carcinoma of the pancreas and cholecystitis). The others were hospitalized for a wide variety of conditions, including cardiac or renal disease (5 patients), obstetric or gynecologic conditions (4 patients), respiratory diseases (4 patients), surgical or orthopedic problems (5 patients) and unexplained fever (4 patients).

The cases among the physicians and nurses developed while they were working and eating regularly in the hospital. The infections among hospitalized patients were found in every building of the main hospital in which patients are housed, including medical, surgical, obstetrical and pediatric wards. At least 1 new case was discovered each month between November, 1948, and April, 1950, except during January, March and May, 1949. On several occasions from 2 to 6 new cases appeared during the same week.

A study of the available data indicated that in 35 of the patients the salmonella infections were probably contracted in the hospital, the first symptoms that could be considered to be caused by this infection beginning several days to several weeks after the patient had been admitted to the hospital for unrelated reasons. There were 15 other cases in which either the acute gastrointestinal symptoms first appeared after the patient had been in the hospital for only two or three days, or in which the symptoms at the time of entry resembled those that developed several days or weeks later in association with the proved salmonellosis. It was considered that these patients had possibly contracted the salmonella infection in the hospital. Only 5 of the patients could be considered definitely to have acquired their infection outside the hospital.

The monthly incidence and probable source of all the cases (that is, whether they were acquired in the hospital or elsewhere) are shown in Figure 1 according to the time when *S. newington* was first isolated in each case. By way of contrast, it is of interest to note that this organism has been isolated only four times during the years 1947, 1948 and 1949 in the Diagnostic Laboratory of the Massachusetts Department of Health,[3] and has not been encountered in the Bacteriological Laboratory of the Boston Health Department[4] during the past few years.

Clinical and Bacteriologic Features

The symptomatology in the majority of the patients was that of acute gastroenteritis. However, a few of the patients exhibited some systemic manifestations, especially at the onset, with prodromata of malaise, weakness and chills. Moderate to severe diarrhea was the outstanding feature, and the most common, among the patients whose signs and symptoms could definitely be attributed to the salmonella infection and not to other disease. Nausea, with or without vomiting, occurred in about half these patients, but usually was not very prominent. Significant fever also was present in half the patients, but varied in degree and had no uniform pattern. In some of the patients, the illness was ushered in by shaking chills, with abrupt rises in temperature to 102 or 103°F.

The duration of acute symptoms, when that could be evaluated, was usually less than four days and often only twenty-four to thirty-six hours. The

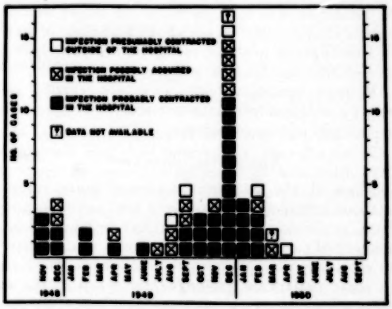

FIGURE 1. *Sources and Monthly Incidence of Cases of Infections with* Salmonella newington.

severity of the symptoms, however, varied greatly. Among 31 patients who had no other complicating conditions, the illness was considered severe in 4, moderately severe in 18 and mild or nonapparent in 9. Some of the older patients who apparently acquired their salmonella infection while they were undergoing treatment for unrelated conditions were particularly prostrated as a result of the infection. Some otherwise healthy young adults likewise had a moderately severe illness, although of short duration. Two patients died, but in neither case could the death be attributed directly to the salmonella infection.

There was no intensive or systematic bacteriologic follow-up study in most of the cases, and no attempt was made to determine the duration of the carrier state. However, repeated stool cultures were made over a period of several weeks in some of the patients. *S. newington* was recovered repeatedly from the stools of several of these patients for periods ranging from eleven to twenty-six days after the first positive culture was obtained, and for at least eleven days after complete symptomatic recovery in 1 case.

An unusual finding was the association of *S. newington* with bacillary dysentery in 5 of the patients, 4 of them children. These 5 patients were admitted to the hospital with characteristic symptoms of dysentery, and *Shigella sonnei* was obtained from culture of the stools at the time of entry in each case. In one of these patients, both *Sh. sonnei* and *S. newington* were recovered from each of 2 separate stools obtained at the time of admission. In the other 4 patients, *S. newington* was isolated from the stools only after sulfadiazine therapy and after the shigella had cleared.

One of the children had a sustained fever with a typhoid-like course. Blood and stool cultures were repeatedly negative until late in the disease, when *S. newington* was isolated from the feces; this patient's convalescent serum showed agglutinin titers of 1:640 against both *Sh. sonnei* and *S. paratyphi B*, and of 1:64 against *S. newington*.

Routine serologic tests were not carried out serially in most of these patients; therefore, this aspect will not be considered.

Antibiotic Therapy*

Most of the patients recovered quite rapidly without specific therapy. In a few patients, however, antibiotics were given either because of persistence of gastrointestinal symptoms or in attempts to eliminate the *S. newington* from the feces. Even in these patients a prolonged follow-up of the results of therapy was not possible. However, data are available on the results of antibiotic therapy in 7 patients.

These 7 patients all received chloramphenicol (Chloromycetin†) by mouth, in divided doses, 2 or 3 gm. per day. In 1 case, the diarrhea stopped during the first two days of therapy, and no follow-up cultures were obtained. A second patient received 26 gm. in eight days, and had negative cultures for salmonella during the period of treatment and throughout a follow-up period of six days. Two patients each received a total of 6 gm. in three days, and the stool cultures became and remained negative during treatment; there was no follow-up study in 1, but in the other the last cultures, obtained four days later, were still negative for salmonella. Two additional patients received similar amounts of chloramphenicol, their cultures likewise were negative for salmonella during the period of treatment and for 4 or 5 days thereafter. In each of these patients, however, *S. newington* was again obtained from subsequent stool cultures. The seventh patient received 11 gm. of chloramphenicol in five days, during which the salmonella continued to appear in the stools.

The latter 3 patients were subsequently given terramycin‡ by mouth, each receiving 5 gm. in three days. Stool cultures, which were positive when this treatment was started, became and remained negative for salmonella during the period of terramycin administration and throughout a brief follow-up period of three or four days in each case.

On the whole, therefore, considering the results in the patients who received no antibiotic therapy, the effects of the chloramphenicol in these cases may be considered to be equivocal. Furthermore, although terramycin appeared to be effective in the 3 patients in whom it was used, the conditions were not really suitable for evaluation of this agent.

Survey of Food Handlers

The epidemiologic evidence suggested that the source of the *S. newington* infections might be inside the hospital. An attempt was therefore made to determine such a source. Because foods such as eggs, poultry and pork, which might be suspected, were supplied from many sources (which were changing continuously), and because these items were always thoroughly cooked before serving, investigations of this aspect did not promise to be very fruitful and hence were not undertaken. However, since all the food for both patients and employees in the main hospital is prepared and issued from a central kitchen, it seemed worth while to examine the employees there for a possible source of the infection. Each of the kitchen employees was therefore interviewed, in order to determine which of them were actually engaged in the handling of food. Attempts were then made to obtain cultures from these food handlers.

This phase of the study was carried out between February and April, 1950. Fecal cultures were obtained by means of rectal swabs, and urine cultures were made from clean voided specimens. It was possible in this manner to obtain cultures on one or two occasions from half of the food handlers. Unfortunately, it was not possible to carry out this part of the study as completely as might be desired, because of the lack of co-operation on the part of the kitchen personnel, since there was no way of obtaining such co-operation except on a purely voluntary basis. None of the female employees of the kitchen staff would co-operate in the bacteriological part of the study.

S. newington was isolated only once — from a single rectal swab obtained from a healthy male food handler.§ About two weeks elapsed before additional cultures could be obtained from this man, but stool cultures were then obtained from him daily for a period of two weeks; all were negative for salmonella. All the cultures from the other employees were also negative for pathogenic enteric bacteria. One can only speculate about the possible relation of positive findings in this one food handler to the cases of infections with *S. newington*

*We are indebted to Dr. George Gee Jackson for most of the observations on this phase of the study.

†Supplied by Dr. E. A. Sharp of Parke-Davis Co.

‡Supplied by Dr. Gladys L. Hobby of Charles Pfizer and Company.

§This man had been working for several years at the same job, which included the handling of food. His serum did not agglutinate *S. newington*.

that occurred in the hospital. It is possible that the positive culture in this case merely represented a transient and nonapparent infection that would have escaped notice but for this survey. It is of interest, however, that no further cases of infections with *S. newington* have occurred at the Boston City Hospital over a period of nine months from the time that these negative stool cultures were obtained from this food handler up to the present.

Discussion

The organism now known as *S. newington* was first isolated by Rettger from ducks in Newington, Connecticut[5] and placed in Group E of the salmonella species in the Kauffmann–White system of classification.[6] That this organism is an uncommon pathogen in man is shown by the fact that in one series of over 12,000 salmonella cultures from a wide variety of sources typed from 1934 to 1947, only 54 strains of *S. newington* originated from man, and 41 of them were from asymptomatic carriers.[2] In another series of 2916 salmonella cultures from man,[1] *S. newington* was found only 11 times, an incidence of about 0.4 per cent; 5 of these 11 strains were obtained from healthy carriers, and all of these isolations were made from stool cultures. The organism has been recovered from spray-dried whole egg powder,[7] from turkeys, chickens, and rats,[2] from lymph nodes of normal hogs,[8] and from infected silver foxes.[9]

There is little clinical information in the literature concerning infections in man from *S. newington*. The organism has been isolated from the blood of man in only one case.[2] Seligmann reported finding *S. newington* in 6 healthy pediatric nurses, in 1 infant, and in a postpartum mother during a mild outbreak of salmonellosis in a hospital nursery.[10] The isolation of a coliform organism with the complete antigenic pattern of *S. newington* from a fatal case of meningitis in a baby has led Seligmann and Saphra[11] to comment upon the possible biologic relation of the salmonellae to lactose-fermenting coliform organisms. Edwards, Bruner and Moran[2] believe that, in contrast to *S. typhi* and the paratyphoid organisms, the animal-adapted salmonellae (that is, those which have been isolated primarily from animals) rarely affect man, do not invade the blood, and are less likely to produce a permanent carrier state.

Felsen, Weil and Wolarsky[12] have recently emphasized the serious nature of outbreaks of enteric infection in hospitals. These authors, who have had extensive experience with the problem of diarrheal disease, have advocated specific preventive and control measures, such as routine monthly stool cultures on all food handlers in the hospital and the appointment of a hospital epidemiologist to carry out these measures. The failure to complete the investigation of the outbreak at the Boston City Hospital because of the lack of co-operation of the kitchen personnel is a characteristic example of the difficulties that may be encountered when there is no adequate authority with organized facilities for dealing with such situations.

A basic feature of any program for control of enteric infections should be a campaign of education among food handlers in the basic principles of food sanitation so that they might understand, accept and practice the methods of prevention and control of food contamination. Hospital food handlers, like those in public eating places, should be under some control and supervision by public-health authorities. In the instance of large hospitals, however, this supervision should be delegated to a competent, duly trained and authorized person who should be given the necessary facilities and who should be responsible for carrying out the necessary control measures.

Summary and Conclusions

A series of 57 cases of infection with *Salmonella newington* was encountered at the Boston City Hospital between November, 1948, and April, 1950. The evidence obtained in these cases indicates that at least 35 and possibly 50 of these 57 cases were part of an outbreak that arose within the hospital. The clinical picture in the majority of patients affected was that of an acute gastroenteritis of varying severity. An incomplete bacteriologic investigation of food handlers in the hospital kitchen yielded inconclusive evidence of the source of the outbreak, although a single temporary carrier of *S. newington* was discovered. The outbreak of salmonellosis described is the largest one due to *S. newington* yet reported in the literature. The importance of preventive and control measures against outbreaks of enteric disease in hospitals is emphasized.

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FIFTY YEARS OF MEDICAL PROGRESS

MEDICINE AS A SOCIAL INSTRUMENT: THE HOSPITAL AND THE COMMUNITY

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CHICAGO

THE relation of the hospital to the community has undergone great changes in the last four centuries. It is scarcely an exaggeration to say that hospitals were set up initially for the primary purpose of abating a nuisance, and that they were operated accordingly for many years. The sick, the crippled, the insane — especially those unable to pay for private care — were public nuisances. The provision of asylum for such unfortunates was as much in the public interest as in the patients' own interest, if not more so. The deplorable conditions in most hospitals, which have obtained almost until our own day, cannot have grown out of concern for the welfare of patients.

Until recently — in the historical sense — hospitals were places in which to die, not places in which to regain health. This prejudice was firmly implanted in the public mind, and it persisted long after I was born. I well remember the difficulties my father encountered in persuading some of his patients that hospitalization was necessary. They regarded it as a death sentence.

This belief was supported by fact. The mortality rate in hospitals was many times that in private homes for the same illnesses. Many factors contributed to this circumstance; increased exposure to infection in the hospital was not the only one.

The discovery of the role of bacteria in morbidity and mortality changed the relation of the hospital to the public in a very short time. Prior to this contribution, the home was the best place for surgery — even for operations of the most serious nature. Even after this discovery, a president of the United States underwent a serious operation on a yacht. Although his choice was prompted primarily by the desire to avoid publicity, it is an indication that the hazards of such an extemporized procedure were not considered sufficiently greater than those of hospital surgery to prohibit the undertaking.

For these reasons, in the pre-Pasteur days, hospitals were essentially institutions for the poor. Government budgets — local, state and Federal — were modest, and most hospitals were privately supported — "supported" in the fullest meaning of the term. Property taxes were low, and there were no income taxes. Persons of wealth regarded hospitals as particularly worthy of their philanthropy.

This situation resulted in certain theories and practices, by some of which hospitals are plagued to this day. The first was that, even after paying patients became numerous, a hospital could not and should not be entirely self-supporting. This is to say that the cost of patient care should not be met in full by direct payments for each case, whether from public sources or from patients themselves. This resulted in acceptance of the principle of deficit financing of hospitals, the deficits to be met through annual contributions from charitably inclined citizens.

Since deficits were usually met without too great difficulty, no effort was made to collect the full cost of hospital care, even from paying patients. This gave rise to an erroneous conception of the cost of hospital operation on the part of the public, and when, because of the drying up of the sources of philanthropy through heavy taxation and devaluation of the dollar, paying patients were rather suddenly required to meet the full cost of their care, the public was shocked by the skyrocketing of the cost of hospitalization.

Since hospitals were operated upon such a hit-or-miss principle, little administrative capacity was required in hospital administrators. Zeal for the cause, moral rectitude, sometimes religious connections and — too often — the need for the job were the only requirements. This was not conducive to efficient management.

Membership on governing boards of hospitals was an honorary appointment, the acceptance of which entailed no personal responsibility for the conduct of the affairs of the hospital. Boards met, at long intervals (sometimes only annually), to place a rubber stamp of approval upon the acts of the administrator and to discuss ways and means of raising funds.

Members of the medical staff came and went as they pleased. Such organization of medical staffs as existed was a matter of form rather than of substance. No attempts were made to control the quality of the professional work, and any effort to do so would have aroused a terrific storm of protest. The medical staffs were merely aggregations of strict individualists, an attitude fostered by the medical profession since the beginning of medical history. As recently as my own intern days, it was unthinkable that one member of the staff should criticize publicly the professional attainments of

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another, although this rule was not applied in private conversations; and there were members of long service upon one particular staff who, as a matter of common knowledge, were not professionally qualified for the work they were doing.

The discovery of the causes and modes of transmission of infection was the first of a series of events that have completely revolutionized hospital operation in almost all its phases, and which have altered radically the relation of the hospital to the community. The introduction of antiseptic, and later of aseptic, technics in hospitals made them increasingly safer places for treatment of patients. At the same time, the necessity for expensive equipment, much of it too heavy to be portable, for the practice of these technics made the home unsuitable for surgery. A large segment of the population suddenly found itself lacking proper facilities for modern surgery — that segment that was able to pay and that previously had had its surgery performed in the home.

This led to a rapid increase in the number of beds in voluntary hospitals. Whereas the greater part of the increase was in beds that brought revenue, the traditional responsibility for the indigent could not be cast aside, and ward beds for "free" patients were always included in any new hospital plans. For some time, beds bringing revenue were occupied largely by surgical patients. Whenever possible, medical illnesses were still treated almost exclusively in private homes. The practice of the private-duty nurse was largely in the home.

The next innovation that enlarged the scope of the service of the hospital to the community was the rapid development of methods of and instruments for precision in diagnosis. First came the roentgen ray, followed in rapid succession (historically) by technics for the measurement of blood pressure and of the basal metabolic rate, and various tests for the functional efficiency of body organs. Some of these procedures could be used in the home; others required proximity to heavy equipment or to an expensively equipped clinical laboratory. Thus more and more illnesses of a medical (as distinguished from surgical) nature demanded the facilities of a hospital for proper care.

The rapid advances of the past few years have further increased the need of an adequate workshop for the diagnosis and treatment of disease. Roadside repairs served the purpose when automobiles were simple mechanisms; but the addition of self-starters, radios, heaters and automatic transmissions has made a machine shop necessary for proper maintenance — not that the human mechanism is any more complex now than it was a thousand years ago, but our understanding of its complexities has increased so greatly. It is not so long ago that the human being who could not be repaired at the bedside by one mechanic with a small bag of tools was towed away, feet first, to the junk yard.

The increased demand for hospital care is not entirely the result of improvement in medical care. Another — and entirely unrelated — influence has come into the picture. This is the profound change that has been effected in the economy of the average home. Only a generation or so ago, spaciousness was regarded as essential to a comfortable home. There were rooms for the family, rooms for guests, and rooms for servants. Sickness could be isolated without difficulty — whether for sanitation or for convenience.

Domestic servants were plentiful and obtainable at wages within the budget of families of modest incomes. Wives were rarely employed outside the home, and neighboring wives were happy to help each other in times of need. In the severest cases, a family could employ a registered nurse without mortgaging the house. In such circumstances, the care of a sick member of the family was not an impossible undertaking.

Today, with apartments becoming smaller and smaller, with living-room furniture doing double duty at night, with domestic service limited to a cleaning woman once a week, with all adults in the family employed, with registered nurses more expensive than business executives, and with total strangers as next-door neighbors, the sick person who cannot attend to his own needs is compelled to turn to the hospital. Thus the relation of the hospital to the community has changed from that of a luxury to that of a necessity.

Still more recently, another influence has risen to increase the demand for hospitals. This is voluntary insurance against the costs of medical care. When such protection is carried, it is perhaps a human trait to exploit it. Someone has said that there is a curious defect in our moral code that makes it no crime to defraud an insurance company. The instance of so-called health insurance appears to support this contention. Too often, and perhaps without realizing that he is abusing his privilege and thereby raising the cost of insurance, the protected person demands hospitalization for causes not specified in the benefits. It is not easy for a physician, however conscientious, to oppose such a demand. The constantly increasing utilization of the benefits of voluntary medical-care insurance has added to its cost almost as much as has the rising cost of hospital operation.

So much for one changed relation of the hospital to the community — the change from an institution shunned by all who could pay for home care into one that is playing a part in the daily lives of a large number of the population.

It might be thought by some that the great improvement of hospital administration in the past few years is wholly the result of the pinch in hospital finances. Although it is true that most of today's formal training courses in hospital administration have been started within the last ten or fifteen

years, there has been a gradual improvement in hospital administration over a longer period than that.

I think that few, outside hospital circles, are aware of the great contributions of the American Hospital Association to the improvement of hospital management. Although not so dramatic as some in the medical field, these contributions are worthy of a place among the great advances in the quality of medical care over the past twenty-five years. Education of hospital administrators has borne fruit more quickly, perhaps, but I think that the education of hospital trustees, while a slower process, is having, and will continue to have, a much greater influence upon the relation of the hospital to the community.

Governing boards of hospitals are accepting, increasingly, their responsibility to the public. Several court decisions, none of which has been reversed, have held that the governing board of a hospital is responsible for all phases of hospital operation. This has posed one very large problem. With rare exceptions, hospitals boards are composed exclusively of non-medical persons. How can such a board discharge that part of its responsibility that pertains to the quality of medical and surgical practice in the hospital?

Some hospital boards continue to ignore this part of their responsibility. Others have attempted to discharge it by dictating to the medical staff in professional matters. This is not only dangerous to patients; it is fatal to the success of the hospital. The only way that offers any hope of success (and the only proper way from any point of view) is to delegate the necessary authority for the discharge of this part of the responsibility to the medical staff itself — and please note that it is the authority to *discharge* the responsibility which must be delegated — not the responsibility itself, which cannot be lifted from the board.

In this, as in other aspects of its duties, the board stands in the position of the board of directors of any large enterprise. No competent board of directors attempts to carry out the details of a business. Instead, the board selects executives in whom it has confidence to fill executive and technical positions. The wise hospital board selects a medical staff in whom it has confidence, and places in the hands of this staff those duties of hospital operation that pertain to medical and surgical practice.

This reliance upon the medical staff must not be lessened through interference from the board. It is a well-known fact, among doctors at least, that many laymen are not good judges of the professional competence of physicians. There is a common tendency to evaluate physicians largely upon the basis of personality — and, in some cases, to accept the physician's estimate of himself. It is difficult for one doctor to deceive another in the matter of professional ability. (A good guide for the selection of a family physician is a doctor's choice of a colleague to care for himself and his own family.)

Thus, if the medical staff is to be held accountable for the quality of medical and surgical practice in a hospital, it must be given a large degree of authority in the selection of its own membership. Just as personalities and personal likes and dislikes may unduly influence a member of the hospital board, so may they influence some of the medical staff; but medical staffs ordinarily are much larger than hospital boards, and such prejudices carry much less weight in the composite judgment of a large group. It is dangerous in either case for one or two forceful members to dominate the group and to exercise undue influence upon the judgment and actions of the others.

To exercise control of the quality of medical and surgical practice, the staff must be properly organized. There should be a chief, or president, of the staff, and departments or services organized according to the specialties represented, each with its chief; and a competent pathologist (in many ways the most important member of the staff) — on full-time duty, if the size of the hospital justifies it.

Regular meetings of the medical staff are essential. In large teaching hospitals, departmental meetings are often substituted for some full staff meetings, but the programs are similar. At these meetings, cases of interest and importance are reported, analyzed and discussed — particularly those in which the results have not been all that could be desired. It is through such critical self-analysis that the medical staff improves the quality of its own work as well as detects incompetence.

To this point the governing board and the medical staff have been considered as separate groups. Because of the very nature of the organization, they must be separate groups, but the dividing line between their two fields of activity must be crossed and recrossed, if the hospital is to attain its full potential for service to the community. The closest co-operation between staff and board is essential. This degree of co-operation can be attained only through close association. Ordinarily, the membership of the two groups is too large to make joint meetings of the entire groups feasible, although in many hospitals there is an annual dinner meeting attended by all members of both board and staff.

For routine joint meetings, a committee from each group suffices to effect the necessary degree of co-operation. It is a great mistake to assume that the interests of the staff conflict with those of the board. If this is true, there is some fatal defect in the composition of one or the other group, or perhaps of both. Although there may be some difference of opinion upon methods of reaching the objective, the objective itself clearly should be the best possible service to the community. Only through co-ordinated and co-operative effort can this ob-

jective be realized; and only through the frequent meeting of men and women of good will can co-ordination be effected and co-operation obtained.

It appears to me that the greatest obstacle to further improvement of the service of hospitals is misunderstanding between physicians and governing boards. Doctors must not forget that the public has acquired a considerable amount of education in medical matters during the past twenty-five years. No longer is the intelligent layman unable to comprehend all professional matters. It is unfortunately true that some of the information given the public upon medical subjects is highly erroneous, but these errors cannot be corrected in the minds of board members through absent treatment. It is necessary for staff and board to confer in person, and for the staff to clarify those matters which may have confused the board members.

On the other hand, board members must discredit the ancient saw that doctors are poor businessman. In more than one hospital, the medical staff, by effecting economies in ways not apparent to a layman, has eased the financial worries of the board. It is no more reasonable to expect a physician to be an expert certified public accountant than it is to expect a layman to bound Scarpa's triangle, but neither deficiency is any indication of inability to understand principles, and the functions of hospital personnel at that level should be limited to matters of policy that are comprehensible to any intelligent person.

Having disposed of the operational elements of a hospital, let us consider the most important figure in a hospital: the patient. The patient is an individual person insofar as the hospital is concerned only as long as he is its guest. Before he enters, and after he leaves, he is but an unidentified part of the community. This accords with the attitude of the patient or potential patient. To him, too often, the hospital becomes personal only when he is in need of it. Too often, the hospital is regarded as an institution located within the community, rather than as an integral and essential part of the community — an ever-present source of assistance when disease strikes. The good citizen feels a sense of security when he meets a policeman, or when he watches a fire engine speeding along the street. There is something personal about these guardians of his security. He should feel, and he must be made to feel, similar contentment when he passes his community hospital.

Until the community, individually and collectively, comes to regard hospitals as assets to be preserved at all costs, and broadens the base of its assistance to include not only voluntary support of community chests and individual contributions but also adequate compensation for the care of public charges, hospitals must struggle as best they can against rising costs. If this struggle is lost (a present danger in some areas), we may expect the Government to take charge of our voluntary hospitals.

We face no greater domestic disaster than Government-controlled medical care. This would sever completely the relations of the hospital with the community. Already, in England, we have seen general hospitals, which have long served all needs in their communities, changed overnight into specialized hospitals to serve large areas. This may promote business efficiency, but it destroys the most important element of good medical care — the personal element. Although business methods have become essential in hospital operation, they must be confined to the storerooms and accounting offices. Once they are introduced into the wards, the hospital ceases to be a servant of the public and becomes its master.

Broadly speaking, the hospitals of the United States are the finest in the world. Several factors have contributed to their excellence, not the least of which has been the Hospital Standardization Program of the American College of Surgeons over the past thirty years. This program has been one of education and encouragement, rather than one of enforcement of arbitrary rules. Standards have been raised repeatedly throughout the years, but only as communities were able to meet them.

So long as hospitals continue to be community projects and so long as communities accept hospitals as community responsibilities, the quality of medical care will continue to improve — but only so long as these two conditions prevail. Too many of our people have yet to learn that Government always takes more than it gives — that we pay an excessive price in liberty, in quality of product, and even in dollars, when we transfer to Government the responsibilities that are in essence those of the community.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 37071

PRESENTATION OF CASE

A sixty-nine-year-old cobbler entered the hospital because of pain and swelling of the right knee.

About three years prior to admission the patient noted "soreness" in the lower end of the right thigh. The pain was intermittent, was worse "when the weather changed" and was thought to be "rheumatism." About six months before entry he first noted that the right thigh was swollen, with severe itchiness of the overlying skin. He also had some difficulty in extending the leg, because of pain and a sensation of "clicking" in the knee.

Previously he had been in excellent health, except for "malaria" of two months' duration that he had had in Italy at the age of seventeen years.

Physical examination revealed a well developed, well nourished man in no acute distress. The superficial lymph nodes were not enlarged. The lungs were somewhat emphysematous; the heart was not remarkable. The abdomen was negative. The skin showed reddening and some heat over the right knee and upper leg. There was diffuse symmetrical enlargement of the distal third of the right thigh, which extended to the knee but not beyond. No specific mass could be outlined, as the enlargement merged with adjacent tissue. The knee joint did not appear to be involved, although it contained an increased amount of fluid and the patella could be ballotted. There was a 10° permanent flexion deformity of the knee, with further flexion to 125°. Palpation of the mass disclosed a smooth, regular surface that was firm but not hard. When the knee was moved, palpation of the mass produced an irregular, lumpy sensation, as if two uneven surfaces were being apposed. The mass was not appreciably tender to touch. The other joints were not remarkable.

The temperature was 98.6°F., the pulse 90 and the respirations 20. The blood pressure was 135 systolic, 85 diastolic.

Examination of the blood disclosed a hemoglobin of 13.4 gm. and a white-cell count of 8000. The urine had a specific gravity of 1.028, and the sediment contained a few white cells and very few epithelial cells per high-power field. The serum total protein was 6.64 gm. per 100 cc., with an albumin-globulin ratio of 1.7, the nonprotein nitrogen 26 mg. per 100 cc. and the carbon dioxide 28.9 milliequiv. per liter; the alkaline phosphatase was 3.2 units, the acid phosphatase 1.3 units, the calcium 9.2 mg. and the phosphorus 3.2 mg. per 100 cc.

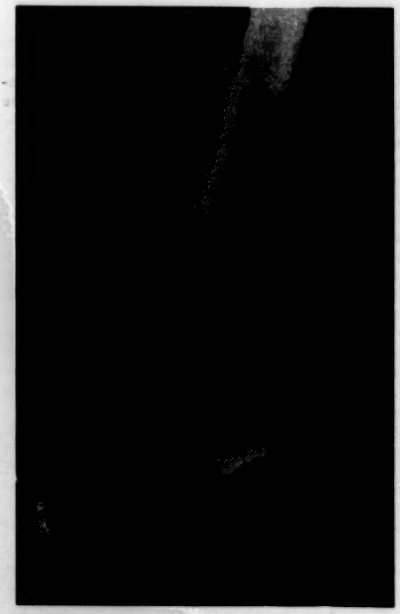

FIGURE 1.

Roentgenograms of the chest showed the lungs to be clear, the heart prominent in the region of the left ventricle and the aorta tortuous. X-ray films of the distal femur and knee joint disclosed a soft-tissue mass extending an estimated 18 cm. proximally from the knee joint (Fig. 1). The mass appeared globular in shape, overlay the anterior surface of the distal femur and extended medially and

laterally to a maximum width of 9 cm. Normal soft-tissue shadows and planes were visible posteriorly but had been obliterated anteriorly. The mass did not extend beyond the joint line and did not involve the femur or patella. No soft-tissue calcification was apparent.

On the seventh day, through a 10-cm. medial incision that extended distally as far as the adductor tubercle, normal subcutaneous tissue, fascia and vastus medialis muscle were observed. The muscle was split in the direction of its fibers and a smooth-surfaced but nodular mass was identified. This mass could be freed medially, superiorly and laterally but was adherent to the quadriceps tendon superficially and to the femur internally. The mass was entirely restricted to the quadriceps pouch. A biopsy was taken.

Differential Diagnosis

Dr. David Grice*: A patient sixty-nine years of age is somewhat older than those I am accustomed to see at the Children's Hospital. However, when I was at the Massachusetts General Hospital I did see some older people on occasion.

May we see the x-ray films?

Dr. Stanley M. Wyman: The chest is well described in the protocol, and there is nothing I can add to the description. It looks normal for a man of his age.

The soft-tissue fullness in the anterior extremity of the lower thigh coming down to the patella is well outlined, seems smooth and extends more medially than laterally. It seems homogeneous, no nodularity can be seen and there is no evidence of abnormal calcification within the mass. The bones are slightly osteoporotic — perhaps from disuse. The joint space of the knee and also the bones show no localized disease otherwise.

Dr. Grice: Do you see anything in the articular or periarticular structures that would account for the pain this man had three years before the present illness — any arthritis or osteolytic reaction?

Dr. Wyman: The joint surfaces, the femoral condyles, and the joint space are apparently normal for a person sixty-nine years old. I do not see anything to account for pain.

Dr. Grice: Do you see anything in this mass that would make you think that there could be fluid within it?

Dr. Wyman: That could be all fluid. If so, there is an extremely large amount. I suspect that it is largely soft tissue, but there is no way to tell by x-ray examination.

Dr. Grice: You could differentiate it from fluid within the suprapatellar pouch?

Dr. Wyman: No; I cannot differentiate this from a huge accumulation of fluid.

Dr. Grice: What about the soft-tissue planes of the muscle? With the fluid within the suprapatellar space, would you expect to see the shadow of the quadriceps tendon and quadriceps muscle distinctly outlined above it?

Dr. Wyman: I believe you can make that out in the lateral view. I think the tendon of the quadriceps can be seen coming down anteriorly at this point.

Dr. Grice: You can see a little increased density that would make you think the mass was lying beneath the quadriceps in that area and within the suprapatellar pouch. There is no evidence of erosion in the cortical surface of the bone at any point?

Dr. Wyman: No; the cortical surface of the femur looks perfectly well preserved.

Dr. Grice: From the x-ray appearance, I gather that this mass did not extend below the adductor tubercle. It seems to terminate in the anterior extremity of the condyle. Is the patella far away from the condyle or in normal position?

Dr. Wyman: I think it is in normal position.

Dr. Grice: I agree with that. The patella is not displaced. The mass seems to lie within the joint space beneath the quadriceps tendon.

The problem I am confronted with is the differential diagnosis of a mass seen in the x-ray films. If roentgenograms show a soft-tissue mass in the extremity that involves bone, it may be of distinct help. As this mass did not involve bone, I can only tell from the x-ray film whether it is a homogeneous mass, whether it obliterates normal soft tissue and what its relative position in relation to the skin is by the preservation of certain soft-tissue shadows. If the mass penetrates through the muscle and continues out into the subcutaneous tissue, one can see that the normal muscle shadows are obliterated. In this case the quadriceps tendon is seen with normal subcutaneous tissue beyond it, so this was a mass deep to the musculature. However, the x-ray films do not help in determining the character of the tumor itself.

In discussing this problem, I think one arrives at certain conclusions merely by reading the history. What can give rise to a mass in the region of the knee joint? Fluid in the superior patellar pouch is usually located anteriorly, is symmetrical both medially and laterally, and rarely becomes encapsulated on one surface or the other. It would be most unusual for fluid within the suprapatellar area to arise above the adductor tubercle and to extend 18 cm. proximally.

It could have been, I suppose, an inflammatory process of some sort. Could it have been infection that had encapsulated in this area and resulted in scar-tissue fibrosis? Against that is the long history of three years, and then the enlargement of the knee joint itself over a period of six months. The motion within the knee joint amounting to 115° — granted that there was limitation of extension — showed a good free range. Even with an inflammatory mass that was not within the joint, one

*Orthopedic surgeon, Children's Hospital.

would expect to find adjacent muscle spasm, irritation and more fixation of motion. Without a great deal of tenderness in the area, the infection would have to be an extremely low-grade one. Tuberculosis is the most outstanding inflammatory condition that can produce low-grade swellings — but there should be destruction of the articular surfaces and demineralization of bone after this interval. A psoas abscess may become very large and can extend down the thigh, but the psoas abscess that extends down the thigh usually does so above the muscles beneath the fascia, rather than deep along the bone. I think, on the basis of the mass plus the normal temperature and white-cell count, that I can probably rule out an acute inflammatory process or a chronic inflammatory process such as tuberculosis. Myositis ossificans can occur in the quadriceps; it is usually an irregular mass, although in an early stage with hemorrhage such an enlargement might be present.

The next question is whether this soft-tissue mass was a tumor of some sort, and secondly, but most important, whether it was a benign or a malignant lesion. Discussions of masses are somewhat prosaic. These structures in and around bone can produce a great variety of tumors. Those arising from bone are fibrosarcomas and osteogenic sarcomas; and from the soft tissue in the region of a joint, because of its embryologic origin, there arise synovioma from tendon sheath, chondromatosis or osteochondromatosis from synovium and very bizarre complexes — so it is very difficult to arrive at a specific diagnosis without a biopsy. In trying to analyze the type of tumor that might arise here, one very often gets a great deal of help from the operative note regarding the distribution of the tumor. The tumor arose from deep structures, and at operation was adherent to the bone and to the quadriceps tendon. A mass that is adherent possibly has some invasive characteristics. Of the tumors that can arise in that area, I would think first of fibrosarcoma. Fibrosarcoma has a low grade of malignancy as far as its potentiality for rapid growth is concerned, although it has been subdivided into Grades, I, II, III, and IV, so some are more malignant and metastasize earlier. The tumor is found usually in the older age group, with its average incidence in persons between forty-five and fifty years of age.[1] About two thirds of all fibrosarcomas occur in the lower extremities, and half occur in the region of the knee joint. It is well known that the tumor arises from the intermuscular septum and the periosteum in the region of the knee. It increases in size, finally becomes adherent and surrounds vessels and nerves in a local manner. It is late in metastasizing and frequently does not metastasize until after the first recurrence. The fact that this mass had been present for six months would not be opposed to the diagnosis of fibrosarcoma.

Synoviomas commonly occur in the region of the knee joint, and can arise, as I said before, from the adjacent structures. The description of the irregular, lumpy surface that seemed to be felt on motion of the knee makes me think of a tumor that involves the synovial reflexion so that on motion it would rub upon itself. That would lead me to suspect that the mass involved the synovium. Ordinarily, with a synovioma, I would expect more fluid within the joint and more signs related to the joint. Also, the age, sixty-nine years, is somewhat against synovioma, but it has been recorded in the older age group.

I wonder if any aspiration of the joint was carried out?

DR. BENJAMIN CASTLEMAN: None was done.

DR. GRICE: Then I should think that there was probably not a tremendous amount of fluid, or the temptation to put a needle in to recover some cells would have been irresistible.

Among other types of tumors that occur in this region is a neurofibroma. There are various statements that about 15 per cent of neurofibromas become malignant, usually in older patients, but occasionally in patients in the second or third decade. I have seen a malignant neurofibroma in a boy fourteen years of age, with local recurrence and extension into all the surrounding structures, which resulted in amputation. It would be interesting to learn if the man had café au lait spots. Were any described?

DR. CASTLEMAN: No.

DR. GRICE: There were no subcutaneous nodules of any sort present elsewhere in the body?

DR. CASTLEMAN: No.

DR. GRICE: That would reduce the possibility of a neurofibroma. There are other tumors of similar character: for example, the neurinomas. Cutler and Gross[2] have described a large series of these tumors that were not related to von Recklinghausen's disease, which can also arise in the area.

The laboratory work is of no great help toward arriving at a diagnosis, other than to rule out infection. The white count was 4800. The alkaline and acid phosphatase, the calcium and the phosphorus are only of value in that they probably indicate that there was no bone involvement in the tumor.

I suppose I should decide on one of these diagnoses, and I think I can do that only on a statistical basis. A fibrosarcoma is my first choice, because it is a tumor that grows slowly, does become adherent to the intermuscular septum, arises from the femur and does become encapsulated. One of the outstanding difficulties with this tumor is that the biopsy section may look benign: the surgeon sees an encapsulated tumor and tries to remove the tumor from within the capsule. Later microscopical examination of the sections shows a very

active process with invasion of the structures, and local recurrence is very high. It is most common in this area, but I do not see how one can differentiate it from a neurofibrosarcoma.

Clinical Diagnosis

Malignant tumor, unknown origin.

Dr. Grice's Diagnosis

Fibrosarcoma.

Anatomical Diagnosis

Chondromatosis of suprapatellar pouch.

Pathological Discussion

Dr. Castleman: It might interest Dr. Grice to know that the preoperative diagnosis was fibrosarcoma, and that the surgeon crossed it out and wrote "malignant tumor of unknown origin."

Dr. Barr, would you tell us the opinion before operation?

Dr. Joseph Barr: There was great uncertainty about the diagnosis; we were not sure it was tumor. Clinically it was a huge mass; there was not much fluid in the joint. The feeling on palpation was an extraordinary one — as though two rubbery surfaces were sliding on each other.

Dr. Robert E. Funsch: The first operation was really a diagnostic biopsy. Through a medial incision we dissected normal subcutaneous tissue and vastus medialis and came down upon the surface of this mass. The first thing that we noticed was that the mass was encapsulated and seemed irregular and lumpy. As we enlarged the incision, it appeared to be completely confined within the synovial pouch. The fingers could be passed around the mass, both medially and laterally along its edge, as far as the point of adherence to the distal shaft of the femur. Superficially, it was adherent to the quadriceps tendon. We then packed off the area and made an incision. We found a very thick wall varying from 1 to 3 cm. The tissue was gritty and was studded with pearl-grey nodules that had all the gross characteristics of cartilage. The fluid that escaped from the incision did not seem to be under increased pressure; it was apparently normal joint fluid. After removal of a block from the side of the mass, palpation showed the entire suprapatellar pouch to be involved with this process. One could feel the undersurface of the patella, which appeared to be normal for the man's age — a little shaggy, but not abnormal. The mass appeared to involve the entire surface of the patellar pouch.

Dr. Castleman: The block of grossly cartilaginous tissue that Dr. Funsch removed showed microscopically normal-appearing cartilaginous cells. None had the atypical appearance or plump or double nuclei that Jaffe[3] has described as being diagnostic of chondrosarcoma. We therefore made a diagnosis of chondromatosis — a condition that is usually interpreted as metaplastic rather than neoplastic. It corresponded to the cases that Luck[4] has described; in fact, Dr. Barr sent these slides, with a description of the operative findings, to Dr. Luck, who agreed with the diagnosis.

The next operation was resection of this whole quadriceps pouch. This photograph of the specimen shows the extensive cartilaginous overgrowth (Fig. 2). The histologic structure was the same throughout the specimen.

Dr. Grice: As I mentioned in my preliminary remarks, the diagnosis of the type of tumor in the

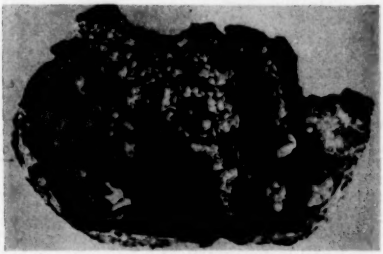

Figure 2.

region of a joint is difficult because of the fact that the various structures have a common embryological origin. The cartilage and the synovia both arise from mesenchymal tissue. The synovia can form both osseous and cartilaginous material. The one finding that made me suspect that this was within the joint was the rough, irregular surface. Chondromatosis is not a rare lesion, but there is usually osteogenesis present that can be seen in an x-ray film. I have never seen a lesion of this size without some bone formation. Whether this lesion should be called benign or malignant is difficult to say on the basis of cell type alone. In dealing with fibrous tissue, connective tissue or osseous structures, one finds that the tumors may have a benign appearance but a malignant behavior. This may have been a metaplasia, but certainly it had grown larger. How would one picture the growth that has taken place? Had each one of these nodules grown bigger, or had new ones developed? We call this metaplasia, but is it not neoplastic as well? I think it is a difficult problem. In regard to treatment at sixty-nine years of age, one would hesitate to do more than a local resection until he found evidence that the process was really malignant. A complete synovectomy would be difficult, if not impossible. Dr. Funsch stated that there was involvement of the cruciate ligaments.

DR. CASTLEMAN: By calling this condition chondromatosis, we avoid the issue of whether it is metaplastic or neoplastic. I do not believe that there will be any distant metastases. As Dr. Grice mentioned, however, they very often become ossified, but there was no evidence of that here.

This man was a cobbler, and he used this knee as an anvil; I wonder whether the constant pounding may have been a factor in the origin or extent of the lesion.

DR. GRICE: The constant pounding of the knee may have been related to the increase in size of the mass in the suprapatellar region, but it would not account for its presence throughout the entire joint synovium.

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CASE 37072

PRESENTATION OF CASE

A thirty-five-year-old woman was admitted to the hospital because of cough.

Five months before admission she developed an upper respiratory infection, with rhinorrhea and irritation of the eyes. A few days later the infection seemed to "settle" in the chest, with a mild unproductive cough and a sensation of having mucus in the chest. Also present were mild pain to the right of the sternum and a sensation of "food sticking in the chest before going down." Two weeks later an x-ray film of the chest showed a suspicious area in the right chest (Fig. 1). A gastrointestinal series was negative. X-ray films of the chest were again taken one and two months later; following the second she was admitted to a tuberculosis sanatorium. In the interim there had been no improvement of the symptoms. She remained in the sanatorium for two weeks, receiving penicillin and streptomycin, apparently with some improvement. Three weeks prior to admission she was admitted to another hospital, where an x-ray examination and bronchoscopy were carried out. No definite diagnosis was established.

During the course of the illness she developed an inconstant deep pain radiating to the right shoulder blade. The mild cough, which had been productive of only a teaspoonful of white sputum a day, was productive of foul-tasting sputum in the two weeks before admission. Hemoptysis had occurred only immediately following bronchoscopy. One week prior to entry she began to have a temperature that ranged from 102 to 103°F., with drenching night sweats. Since the onset of the illness there was progressive mild dyspnea for which she occasionally had to be propped up on pillows to prevent a smothering sensation, an increasingly poor appetite and a weight loss of fifteen pounds.

There were no previous serious illnesses. A course of treatments for gingivitis and pyorrhea had been completed a few months before the onset of this illness.

Physical examination revealed a thin, poorly nourished woman with a nonproductive cough. The tongue was coated. The gums showed no evidence of active inflammation. Loud rhonchi were heard throughout all parts of the lung, with a prolonged expiratory sound. There were no other physical findings of note.

The temperature was 100°F., the pulse 120 and the respirations 28. The blood pressure was 120 systolic, 70 diastolic.

Urinalysis was negative. Examination of the blood showed a hemoglobin of 12.2 gm. and a white-cell count of 11,600, with 74 per cent neutrophils. The nonprotein nitrogen and total protein were normal. The sedimentation rate was 30 mm. in fifteen minutes, 52 mm. in thirty minutes and 56 mm. in sixty minutes. The prothrombin time was 28 seconds (normal, 19 seconds), or 50 per cent of normal. Examination of the sputum was negative for tubercle bacilli and for tumor cells. O. T. (0.1 cc. of 1:1000 dilution) was negative. A blood Hinton test was negative. X-ray films of the chest disclosed extensive infiltration in the right upper lobe, with confluent areas of density in the medial posterior portion of the lobe and somewhat mottled-appearing density in the remainder of the lobe (Fig. 2). Enlarged lymph nodes appeared to be present in the right hilar region and possibly also in the right paratracheal region. There was some fluid within both the major and minor septa on the right. Review of the outside films showed that there was initially a small zone of density within the outer portion of the right second interspace, and adenopathy in the right hilum.

On the tenth hospital day a bronchoscopic examination revealed a normal trachea and carina. The mucosa of the right main bronchus was reddened and edematous. The swelling of the bronchial mucosa was so great that the bronchoscope could not be introduced below the level of the upper-lobe bronchus. The opening to the upper-lobe bronchus was narrowed by swollen and engorged mucous membrane. The mucosa bled easily with manipulation. Material removed at this examination was negative for tubercle bacilli and tumor cells.

On the fourteenth hospital day the patient suddenly coughed up approximately 650 cc. of blood. She died shortly thereafter.

During the hospital stay the temperature varied between 101 and 103°F. the symptoms and signs remained unchanged.

Differential Diagnosis

Dr. Gordon Scannell*: The fact that the bronchoscope could not be introduced below the level of the upper-lobe bronchus because of swelling of the mucosa is very interesting; it suggests that there was extrinsic pressure upon the bronchus.

I should like to ask whether the patient received antibiotics throughout this hospitalization.

Dr. Benjamin Castleman: She was receiving 1 gm. of streptomycin, beginning on the fifth hospital day and continuing for four days. She also received 300,000 units of penicillin on the fifth day.

Dr. Scannell: That she did not respond to antibiotics is important. I suspect the physicians who saw her were as surprised as I am that she died suddenly with the first hemorrhage.

May we look at the x-ray films?

Dr. Joseph Hanelin: The first posteroanterior films of the chest, taken approximately four months before admission, show a zone of density in the outer portion of the right second interspace and quite definite evidence of enlargement of the lymph nodes

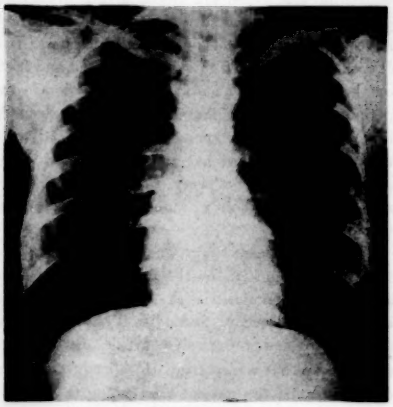

Figure 1.

in the right hilus (Fig. 1). Two months later there is enlargement of the lesion situated peripherally in the right lung, and probably also some increase in adenopathy. The left lung is clear in all the examinations that were done. The next examination, done about a month later, reveals a very slight increase in the peripheral lesion, persistent right-hilar adenopathy and strand-like densities radiating from the right hilus. A rather striking change in the appearance of the chest occurred nine days later (Fig. 2). There is now rather extensive involvement of the right upper lobe, which is not segmental in distribution, although the bulk of the density appears to lie in the posterior medial portion of the lobe. The mass situated in the periphery is still present, although not as well seen as in the preceding films. In addition there is slight displacement of the esophagus below the carina, suggesting the presence of enlarged lymph nodes in this

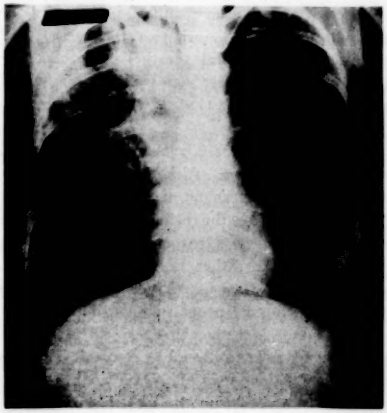

Figure 2.

region as well. The major and minor septa on the right are thickened.

Dr. Scannell: In the original films, can you see any suggestion of bronchiectasis in the right lower lobe?

Dr. Hanelin: No: I cannot.

Dr. Scannell: If it were present, you probably would be able to see it?

Dr. Hanelin: Very often, without any difficulty.

Dr. Scannell: This problem, then, can be resolved into a differential diagnosis of bronchopulmonary suppuration with fatal hemorrhage in a young woman. Terminal hemorrhage in an acute process is unusual. If I approach it on that basis, four diseases come immediately to mind: tuberculosis, adenoma of the bronchus, putrid lung abscess without neoplasm and primary neoplasm of the lung. Any of these conditions might obtain here.

Primary cancer of the lung is, of course, the suspicion that we must have with this picture, and there are several points in favor of this diagnosis. The suppurative process in the right upper lobe failed to clear on administration of antibiotics and on rest. If there were not a neoplasm causing it,

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or if it were tuberculosis, I would expect one of two things to have happened: Either the process should have cleared or shown considerable improvement, or it should have shelled out and become more rapidly fatal. In the second place, the suppuration, which was obviously very severe, occurred without any adequate precipitating illness. Were this in a man given to drunken stupors it would not surprise me, or in a patient who was generally debilitated — but there was no evidence of that. If there had been manipulation in the mouth — extraction of teeth, tonsillectomy or general anesthesia — that might give me a clue, but here was a patient who merely had a "cold" and from that started a chain reaction that ended in death.

The third point is pain, which is quite common in neoplasm of the lung. Although the pain in this patient was usually vague, it suggested pleural involvement. It was in the region of the right shoulder blade. That suggests involvement of the lower intercostal nerve, rather than the so-called Pancoast syndrome. The fourth thing that makes me think of obstructing neoplasm, and a suppuration behind a tumor, is the fact that the process remained quite well confined to one lobe. Had this been nonneoplastic inflammatory disease, I would have expected it to spread from the posterior segment of the upper lobe across the major fissure to the superior segment of the lower lobe. Lung abscess will quite readily do that if it is not controlled, as this apparently was not. Therefore I am inclined to think in terms of something obstructing the lobar bronchus. Weight loss and anorexia go with neoplastic disease. There was evidence also of mediastinal extension that was noted from the very beginning and that had increased tremendously, as seen on the x-ray films. Lymph-node involvement can go with inflammatory disease, but such enlarged lymph nodes are usually soft and do not throttle the bronchus, as occurred here.

Against the diagnosis of primary cancer of the lung are the age and sex of the patient. However, this was an unusual patient, and we do see carcinoma in women — and we see it below the age of thirty-five. There is also the absence of tumor cells in the sputum and in the bronchial aspirations. Although if tumor cells were present it would be positive evidence, the fact that they were not found carries very little weight in the face of an advancing process.

If this was a putrid lung abscess, I should have expected that when this patient began to raise foul sputum she would have shelled out a cavity that could have been seen on the x-ray films. As we mentioned earlier, there was not adequate cause, except cancer, for lung abscess in the patient, although massive hemorrhage is quite consistent with acute lung abscess and is a likely cause in a young patient with a febrile course and disease localized to the posterior segment of the right upper lobe. Without adequate precipitating cause, with failure to improve or to get much worse on antibiotics, with the general picture and sex of this patient, I shall discard putrid lung abscess without neoplasm.

Adenoma of the bronchus classically leads to repeated hemorrhages and pulmonary suppuration. It occurs in women as often as it does in men, and it usually becomes apparent at a relatively early age. Adenoma, however, to cause this picture, would have to be in the hilum, giving rise to obstructive symptoms; and if that were true it should have been seen at bronchoscopy — and it was not. It would be very hard to explain the pain and fever on the sole basis of an isolated round lesion in the periphery, and a peripheral adenoma is extremely rare. Although adenoma may invade adjacent tissues and therefore has a reputation for being malignant, it invades very slowly, and I would not expect it to show so much pleural reaction as this did.

The fourth disease I must consider is tuberculosis. It would be unusual for the patient to have such advanced tuberculosis with a negative sputum, but that could occur. Secondly, it would be most unusual to find progressive febrile disease with tuberculosis that was so clearly localized to the right upper lobe. If the patient were going to die with progressive tuberculosis she would have shown greater spread of the disease prior to death. The tuberculin test in the presence of severe overwhelming tuberculosis might well have been negative. It is often negative and does not help me too much. The bronchoscopic findings were far from consistent with tuberculosis, unless she had a tremendously acute tracheobronchitis; then I would think the process would not be so well localized to one lobe.

There are other diseases that I should consider. I asked Dr. Hanelin about bronchiectasis, because

dry bronchiectasis in the upper lobe is a well known cause of bleeding — although patients with dry bronchiectasis rarely present themselves with a drowning hemorrhage as the first evidence of bleeding. However, there was no evidence of bronchiectasis in that lobe. She could have, I suppose, vomited the blood from an erosion in the esophagus — she had evidence of mediastinal involvement — but there is every reason to believe she coughed up the blood, and I must accept that at its face value.

An aberrant artery could have been present, but it is usually in conjunction with a congenital cyst, and there was no evidence of that. It is extremely rare at best, and hardly would account for all the suppuration that was found. Another alternative, also a rare lesion, is lymphoma of the lung. The one or two cases that we have had here have shown a consolidated lesion of the lobe. I mention it just to cover myself. I shall say that the diagnosis was primary cancer of the lung — probably adenocarcinoma with mediastinal lymph-node metastases.

DR. BENEDICT: I agree with Dr. Scannell.

CLINICAL DIAGNOSIS

Tuberculosis, ?carcinoma of the lung.

DR. SCANNELL'S DIAGNOSIS

Adenocarcinoma of the lung with mediastinal metastases.

ANATOMICAL DIAGNOSES

Squamous-cell carcinoma, Grade III, of the lung, with metastases to regional lymph nodes and pleura.

Massive hemorrhage into lungs.

Bronchiectasis, right upper lobe, with abscess formation.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy here showed a large lesion in the region of the right hilus, which occluded the right-upper-lobe bronchus so that one could hardly see any lumen at all. The bronchi to the lower and middle lobes and that to the left were completely filled with fresh blood, so that the main cause of death was suffocation due to the hemorrhage. There was some blood in the region of the tumor, which was probably the cause of the bleeding. The right pleural cavity was completely obliterated by dense fibrous tissue, and in trying to remove the lung near the apex we found what appeared to be neoplasm adherent to the parietal pleura but not invading the lobes. Distal to the tumor, the upper lobe was made up of distended bronchiectatic cavities, some with abscess formation and some with inspissated secretion, but no definite tumor. The regional lymph nodes were enlarged and apparently involved with neoplasm.

On microscopical examination, this was seen as a Grade III squamous-cell carcinoma, with metastases to the carinal lymph nodes and other lymph nodes in the region of the right-upper-lobe bronchus. The pleura near the apex also showed carcinoma. The pneumonitis and bronchiectasis throughout the entire lobe were very severe, there being no viable parenchyma left. It is very likely that most of the patient's symptoms were due to this acute and chronic infection beyond the obstruction.

DR. SCANNELL: Was there any tumor on the other side?

DR. CASTLEMAN: No; the other lobes in the right lung and the entire left lung were normal, except for the terminal hemorrhage.

We did not have permission for a complete autopsy, but palpation of the liver showed no evidence of tumor, and I believe it may well have been limited to the lung.

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NOSOCOMIAL GASTROENTERITIS

THE hospital outbreak of infections with *Salmonella newington* reported elsewhere in this issue of the *Journal* raises a number of important points of interest that are worthy of comment. At first blush, it seems odd that such an outbreak should occur in a hospital, where people come to be cured of illnesses, not to acquire new ones. Occasional nosocomial infections, however, are almost unavoidable in spite of even the most elaborate precautions. This is particularly true in infants' and children's wards where patients may be admitted with communicable diseases that remain undetected until after they have had an opportunity to spread to other susceptible patients. The spread of respiratory infections, and occasionally of other types of infections, from hospital personnel to patients is only partially preventable by constant vigilance. The acquisition of many infections, including tuberculosis, by physicians, nurses and medical students from patients with open and active lesions is accepted among the hazards of the medical and nursing professions, just as occasional laboratory infections are expected among bacteriologists who deal with infectious materials.

Gastrointestinal upsets, with nausea, vomiting and diarrhea and sometimes with fever, but usually of short duration, are quite common among hospitalized patients, and in hospital personnel as well. In the patients, these upsets are often brushed off as due to intolerance to some food or medication, or they are considered part of the symptomatology of the underlying illness. In the hospital personnel, bouts of gastroenteritis are usually taken for granted, as in the category of complaints about the quality or quantity of food that is served. In hospital workers, these upsets may be a source of considerable discomfort, often resulting in loss of efficiency, but in severely ill and debilitated patients they may seriously interfere with recovery, or they may result in interruption or decrease in efficiency of some essential therapeutic agents, at times even being the immediate cause of a fatal outcome.

Careful study of these cases, however, will usually reveal the fact that such upsets, like most similar ones throughout the community, represent gastrointestinal infections resulting from the ingestion of infected foods. The determination of the nature of the infectious organism requires alertness and zeal on the part of the physician, the co-operation of both patient and physician to obtain suitable specimens for cultures and the proper bacteriological handling of the specimens. The detection of the source of the infecting organism requires, in addition, accurate identification of the causative agent and diligent epidemiologic searches. These, in turn, require the co-operation of the clinical and laboratory staff, of the hospital administration and of all persons concerned with the handling of food.

A large part of the credit for the recognition of the outbreak of salmonella infections here reported from the Boston City Hospital must go to the enthusiastic and energetic staff of the bacteriology laboratory of the Mallory Institute of Pathology, and

to the high standards of performance that they are able to maintain in spite of the tremendous volume of work they are called upon to do. The epidemiologic studies that were carried out in an attempt to determine the source of the infections had the interest and support of the hospital administration. The authors, however, found that their efforts were hampered by the failure of many of the food handlers to co-operate in helping to track down those among them who might have been responsible for maintaining the infection within the hospital for so long a time.

This particular outbreak seems finally to have ended, possibly because of the spontaneous disappearance of the offending organism from the one carrier who was detected among the food handlers. Furthermore, although many cases undoubtedly went unrecognized, and although some of the patients who were studied were seriously ill, the total number of recognized cases was not very large, and the outbreak, on the whole, may be considered not very serious. Such an outbreak, however, if it had been produced by more virulent organisms, might have caused considerably more illness, and even deaths. The authors, therefore, justifiably call attention to the fact that the authority is lacking to enforce co-operation in epidemiologic studies that in other circumstances might be essential for the control of serious infection.

A hospital, in addition to its function in the care of the sick, also serves as a hotel; it must feed not only the patients, but a large supporting staff. The need for bacteriologic control of food handlers in hospitals may be considered of even greater importance than in the case of hotels and restaurants. The authors, therefore, support a suggestion made by Felsen, Weil and Wolarsky* that specific preventive and control measures be taken in all hospitals. These would include routine monthly stool cultures of all food handlers and the appointment of a hospital epidemiologist to carry out these measures. An alternative, and perhaps a preferable one, would be the assignment of an epidemiologist from the local or state health department to each of the hospitals. This epidemiologist would be required to make periodic visits to the hospital, and make the acquaintance and obtain the co-operation of the clinical and laboratory staffs. He would collect materials for culture, and would also survey the entire problem of infections within the hospital to which he is assigned. Such an arrangement would keep the public-health authorities in constant touch with serious infectious diseases that are prevalent in the community, through the patients who are in hospitals and whose illness can therefore be readily studied and diagnosed.

The epidemiologist in this instance should have authority, exercised perhaps through or with the help of the hospital administration, to require food handlers to submit to whatever cultural procedures are indicated. The fact that such authority is available to him would usually be enough to obviate the need for using methods other than those of simple persuasion when the health of everyone in the hospital is at stake. Moreover, the epidemiologist would be responsible for the education of the food handlers in the recognition of infected foods and in the elementary principles of personal hygiene and sanitation upon which the prevention of food infection so largely depends. The epidemiologist would also be on the alert to help in the control of epidemics other than those resulting from food infection, by assisting in the investigations of the causes and sources of epidemics. He would also be helpful to the clinical and bacteriologic staff of the hospital by keeping them interested in maintaining high standards of diagnosis and by constantly impressing upon them the importance of their activities in the prevention of diseases in the community.

*Felsen, J., Weil, A. J., and Wolarsky, W. Inapparent salmonella infections in hospitals. *J. A. M. A.* 143:1135-1138, 1950.

THE CRIPPLED AND HANDICAPPED

The days preceding Easter are those during which the "seal sale" of the Bay State Society for the Crippled and Handicapped will be conducted; it is a worthy campaign, for which the utmost success is to be wished.

The Easter Seal Sale will be inaugurated this year with a Bay State Rehabilitation Conference, to be held at the Copley Plaza Hotel, in Boston, on February 21. At that time rehabilitation projects in Springfield, Worcester and Boston will be dis-

cussed and demonstrated, and packets of Easter seals will be distributed to over a million Massachusetts families.

The entire program of the Bay State Society is supported by the money raised by means of the campaign, from which a fund of $292,000 must be realized.

This may be considered yet another campaign among the many that take place each year, but until some effective mutual organization is perfected, each project must be supported to the limit of the communities' charitable tolerance.

THE FEWER, THE MERRIER

PROGRESSING from the commonly accepted belief that three's a crowd where two is company, Nicolas Rashevsky, professor of mathematical biology at the University of Chicago, has gone more deeply into the matter.

Professor Rashevsky, adopting the usual definition of *crowd* as "a large number of persons collected into a close body without order," rather than as an ancient six-stringed Celtic musical instrument, as Webster's Collegiate Dictionary, Fifth Edition, also holds, has derived a mathematical equation to answer the question of how many people make a crowd.

It appears that it depends, according to a recent release from the University of Chicago Office of Press Relations, on the circumstances. The study begins with an analysis of the activities, the thoughts, the fears and the moods of the individual, expressed mathematically. Taking the "imitation factor" into consideration, it becomes possible to demonstrate mathematically that the crowd as a whole may pursue a particular activity despite the fact that the majority of individuals in it may prefer something different.

It takes more of a certain type of person and fewer of another type to make a crowd. One thing is sure: However noble or ignoble their strife may be, crowds are undoubtedly madding. Many persons prefer to keep their own way, with or without a noiseless tenor for accompaniment.

The Diary of a Tobacco Smoker and Chewer. — . . . . . *which is said to be the veritable diary of the Rev. Solomon Spittle. The dedication is from the pen of Dr. Ziba Sproule, who states that he made the post-mortem of Spittle, and thinks there is no doubt that his death was "Phthisis, caused by the inordinate use of tobacco."*

Boston M. & S. J., *February 19, 1851*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

JANES — Arthur P. Janes, M.D., of Boston, died on December 30. He was in his seventy-second year.

Dr. Janes received his degree from Tufts College Medical School in 1905. He was a fellow of the American Medical Association.

His widow, a daughter and a granddaughter survive.

CORRESPONDENCE

MORAL OBLIGATION

To the Editor: Regarding the letter from Dr. Thomas R. Goethals published in the November 30 issue there is some need for refutation and amplification. Although I have the highest personal regard for Dr. Goethals, having been under his command in the last war and later having had him as an instructor in medical school, I consider his statements inexact and misleading.

Furthermore, I deeply resent the aspersion cast on the character and patriotism of those who received training in the ASTP. The theme of "moral obligation" has been too long used as a recruiting tool and thrown in the faces of those once in the ASTP or V-12 program. Lightly regarded is the fact that many of these persons served in the troops, and even overseas, before or during enrollment in college training courses. This was especially true of men who graduated from medical schools in 1949.

Perhaps this is also the time to reappraise the philosophy of such programs as the ASTP. Firstly, these were organized to provide a steady increment of skilled men to meet the needs of a rapidly expanding military establishment. But, secondly, and I think of much greater significance, it was a means of conserving a cadre of men of intellectual potential for the future needs of the nation. One readily recalls the effects on France and England of having an entire generation decimated in World War I. Also, the value of such programs is demonstrated by the Navy's recent decision to expand its ROTC establishment.

The nation's experience in three major wars has thoroughly attested to the merit of selective service as the only means of equitably evaluating men for military duty. However, prior to the present grave international picture I believe that the response of former ASTP and V-12 students to the call of the services was much greater than is indicated by Dr. Goethals.

As an example of the above, last summer, while en route overseas, I met two former ASTP classmates at the port of embarkation on the way to Europe. We were not alone, there being others on the way at the same time. Also, currently I share the duties of a large consolidated Air Force and Navy medical installation with two Navy medical officers, both former V-12 students.

Lastly, I believe that a more sympathetic attitude should be shown men remaining in residency training or newly established practices. Most often to do so aids the common good more than a wild leap into the chaos of military expansion. Wisdom dictates that one select with care and discretion, rather than decide on an emotional basis to sweep physicians into the service.

James S. Cheatham
Captain USAF (MC)

APO 863
% Postmaster, New York City

Captain Cheatham's letter was referred to Dr. Goethals, whose reply was as follows:

To the Editor: Captain Cheatham has evidently overlooked or disregarded the fifth paragraph of my previous letter, which referred to ASTP's who had not seen fit to repay their obligations for medical training at Government expense in World War II by serving in the armed forces. The subsequent paragraphs, by context, referred to this group. The figure of one (1) ASTP volunteer out of three thousand (3,000) who had not served in the armed forces was obtained from *Capitol Clinics*, No. 34, published by the American Medical Association on September 5, 1950.

Captain Cheatham maintains that the ASTP program constituted a means of conserving a cadre of men of intellectual potential for the future needs of the nation. If this was generally understood by graduates of the program, it is hard to explain why these men did not understand that the needs of the nation for their services last summer were immediate and pressing, and not postponable to the future.

Captain Cheatham is to be complimented on recognizing and acting upon his own moral obligation, even if he doubts the validity of such a concept when applied to those who received training under ASTP in general.

Thomas R. Goethals, M.D.

Boston

CHOLESTEROL METABOLISM IN THE RABBIT

To the Editor: In a paper on xanthomatoses in the *Journal of the Mt. Sinai Hospital* (17:79, 1950) Dr. S. J. Thannhauser states that "herbivorous animals are unable to excrete animal sterols. The animal sterol is retained and hypercholesteremia develops. Herbivorous animals, therefore, should not be used for comparative experiments on cholesterol metabolism." Since an abstract of this paper appeared in *Modern Medicine*, which is distributed widely among clinicians, the medical profession is entitled to a knowledge of the facts in this connection.

The rabbit is a herbivorous mammal, producing cholesterol—animal cholesterol — as the mother substance for its adrenocortical and sex hormones and for other purposes. It differs from man in that its animal cholesterol is synthesized, since its diet contains no animal cholesterol. Not only can atherosclerosis be produced in its arterial system by the feeding of cholesterol, but also it can be prevented by the addition to the cholesterol feeding of thyroid substance or, less constantly, of potassium iodide, as demonstrated by K. B. Turner in an article entitled "Studies on the prevention of cholesterol atherosclerosis in rabbits" (*J. Exper. Med.* **58**: 115 and 127, 1938); in other words, the same amount of cholesterol fed by mouth that will induce atherosclerosis in rabbits is taken care of by the cholesterol metabolism of a rabbit that is also receiving thyroid substance, without the production of atherosclerosis. The cholesterol metabolism of the animal is dependent on thyroid control, as in human cholesterol metabolism, which is associated with little or no atherosclerosis in hyperthyroidism and with advanced atherosclerosis in hypothyroidism. Further evidence of the constancy of thyroid control of the cholesterol metabolism in mammals appears from the production of atherosclerosis in dogs, in which animals the disease does not follow massive cholesterol feedings, as described by Steiner and Kendall in an article on the subject "Atherosclerosis and arteriosclerosis in dogs following ingestion of cholesterol and thiouracil" (*Arch. Path.* **42**:423, 1946). The disease was produced by cholesterol feeding associated with the use of thiouracil to damage the thyroid gland. It is apparent that cholesterol metabolism in the rabbit, in man and in the dog is controlled by thyroid secretion. The rabbit and the dog represent, perhaps, two extremes with reference to the potency of the cholesterol metabolism, but no doubt remains that the cholesterol metabolism in both animals is not dominated by the question of cholesterol excretion.

Animal experiments have their principal use in clearing up the causation of human disease. We select animals in which a given suspected agent exhibits pathogenesis. If the animal is susceptible does the given agent reproduce the lesions of the human disease? We can kill animals at will and thus add to our information about the method of action of the given pathogenic agent in producing a disease. This may throw light on the method of production of the human disease. Does the rabbit satisfy requirements in respect to the questions it may be called upon to satisfy?

Excess cholesterol in the rabbit is a pathogenic agent. It stimulates the growth of tissues, particularly connective tissue. It causes lesions in the rabbit's arteries that reproduce to a remarkable degree the lesions of human atherosclerosis. The steps in the evolution of the disease can be followed, because of the esterification of the excess cholesterol in the liver, to which Thannhauser and Schaber drew attention in their study entitled "Relation of equilibrium between cholesterol esters and cholesterol in blood and serum to liver function' (*Klin. Wchnschr.* **5**:252, 1926), and the distinctive character of the ester crystals, which are visible under polarized light, as pointed out by Leary in his article on the subject "Crystalline ester cholesterol and atherosclerosis" (*Arch. Path.* **47**:1, 1949). Excess crystals are deposited in liver cells, from which they are engulfed and removed by Kupffer cells in the liver sinusoids. They are transported in the Kupffer cells into the circulation, and are carried into the subendothelial layer of the arterial intima, where they induce the lesions of atherosclerosis.

There can be little doubt that the rabbit is a suitable animal for comparative experiments on cholesterol metabolism.

Timothy Leary, M.D.

Boston

INFILTRATION ANESTHESIA

To the Editor: At the meeting of the Board of Registration in Medicine held January 25, it was voted to revoke the registration of Dr. Claude G. Shepherd, 219 Branch Street, Lowell.

Robert C. Cochrane, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

INFILTRATION ANESTHESIA

To the Editor: I have the honor to send you this letter with my sincere respect for you and your journal.

I am one of the most enthusiastic readers of the *New England Journal of Medicine* and deeply interested in the many excellent articles.

In the number of October 26, I find an article by Dr. Archie A. Abrams entitled "Obliteration of Pain at the Site of Reference by Intradermal Infiltration Anesthesia in First-Stage Labor."

The mentioned principle and method was already published by myself on January 10, 1947, at a medical meeting here and since then published on several occasions.

As it was never published in a foreign language, I suppose that his studies have started from his own originality, but at the same time I know he will be generous enough to pay attention to my priority in this reference. Of course I thank him for the agreement of both conclusions and never wish any injustice.

I am sure my studies are not known to him, so I should be pleased if you could send him this note and in consequence I could make his acquaintance.

I am not an obstetrician, but a specialist in surgery and orthopedics; hence, these references are nothing but a relatively minor part of my extensive investigations, and the chief subject was concerned with the entire physiological and surgical problems.

My theory was entirely contradictory to the classic and current views among all the scholars and authors in this country and thus met with curiosity, but now I believe that there is no need to convert even a mere trifling part. My theory is established on confirmed human experiences, con-

trary to those deduced from animal tests, which are absolutely misleading in such problems.

At that time I saw that continuous caudal anesthesia was becoming widely prevalent in the United States, but the theoretical interpretations of the introducers were completely erroneous.

Also the views presented by most influential physiologists and surgeons in the United States regarding visceral sensibility are divergent and generally irrational.

Many surgeons are seemingly hardly struggling against various so-called intractable pains and are inventing more and more complicated operations, as well as the internists many remedies.

Generally speaking United States medicine takes seniority over the Japanese, but as I see it, I have almost ten years seniority of the former in this regard.

Thus I have wished to publish my views at some medical meeting in the United States and sweep away all sorts of so-called intractable pains from the country, but I am, to my great regret, not yet favored with such occasion and means, and I fear the coming war will distubr it forever.

Even if I and you are separated by the Pacific Ocean I trust your faith and sincerity.

And I should be much obliged to you if you could publish this note in your *Journal* and send it to Dr. Abrams.

HIDEO WAKAHARA, M.D.
Chief of Surgery
East City Hospital
Higashi-ku, Oska

Dr. Wakahara's letter has been referred to Dr. Abrams, who makes the following reply:

To the Editor: I am indeed happy to answer the above communication from a colleague in Japan. It might not be amiss to indicate that Drs. Soma Weiss and David Davis, in a series of experiments performed on human beings published in 1928, concluded that visceral pain is in reality a viscero-sensory reflex, as postulated earlier by MacKenzie and others. In 1928 Dr. David Rose described the success of intradermal use of novocaine to break the pain-reference arc in the first stage of labor. Unfortunately, the publications of Dr. Wakahara are not known to me and I have since communicated with him requesting reprints of his work. That our conclusions are in agreement is most gratifying.

ARCHIE A. ABRAMS, M.D.

BOOK REVIEWS

Clinical Sonnets. By Merrill Moore, M.D. 8°, cloth, 72 pp. New York: Twayne Publishers, Incorporated, 1949. $2.50.

The followers of Aesculapius have long been noted for their accomplishments in the arts, — their skill with brush and palette, — and, on several occasions, exhibitions devoted entirely to works by physicians have been organized. Those who have become devotees of the poetic muse are less numerous, but their roster from the time of Albrecht von Heller to the present has contained many names, distinguished both in medicine and literature. Oliver Wendell Holmes and Silas Weir Mitchell are names of which Americans are justly proud. In the contemporary period Dr. Merrill Moore has devised a sonnet form that is significant both of America and the time he lives in, and sonnets from Merrill Moore's pen will have their place in the permanent literary legacy of this country.

Dr. Moore, in this most recent volume, shows an astonishing and mature insight into human nature. He has been able, in the limited space permitted by his chosen form, to create unforgettable sketches of the personalities that have crossed his path. As his title indicates, Dr. Moore has frequently chosen his subjects from among his patients, and in order to create, as he has done with extraordinary facility, a personality in one hundred and twenty-five to one hundred and fifty words, every character trait had to be etched in almost with overemphasis — yet they are true to life. Who has not met a "Dr. ABCD . . ." or found among his friends the inherent beauty of the character depicted in "She Was a Fertile Woman, a Garden of Herself"?

Some of these sonnets are startlingly frank; some — notably "Item: murder" and "No comment" are as hard-bitten and sinister as a William Faulkner short story. Not all are character sketches — there is a wealth of philosophy in "He said: I believe that change is the aftermath." There is not a dull line in the book.

Electrocardiography: Fundamentals and clinical application. By Louis Wolff, M.D. 8°, cloth, 187 pp., with 110 illustrations. Philadelphia: W. B. Saunders Company, 1950. $4.50.

This is a practical instruction book for the beginner or the moderately advanced student, having the virtue of taking him in steps through logical explanations of the electrical phenomena of the heart beat. Its basis is the long experience of the author as a teacher of electrocardiography to undergraduate and graduate students.

The first part gives the basic principles of electrical properties of the cell membrane, dipoles, vector representation, volume conductors, T-wave changes, ventricular gradient, precordial, limb and unipolar leads, bundle-branch block, ventricular hypertrophy, currents of injury and myocardial infarction.

The second part, discussion of clinical electrocardiography, covers the normal electrocardiogram, bundle-branch block, right and left ventricular hypertrophy, coronary-artery disease and myocardial infarction, pericarditis, pulmonary embolism and the Wolff-Parkinson-White syndrome.

The contents of the first part, when really digested by a student, should make him able to apply principles to clinical interpretation under all conditions, thus converting the reading of electrocardiograms into an exercise of reason and not simply the recollection of memorized patterns.

The author considers "left ventricular strain" as an incorrect term and prefers "left ventricular hypertrophy" and attributes T-wave changes to hypertrophy. The ability at times to reverse instantly such inverted T waves by drugs lowering the blood pressure, such as Protoveratrine, appears to the reviewer to justify the retention of the term "strain" in electrocardiographic nomenclature, since it is inconceivable that ventricular hypertrophy is altered by such a transient effect.

Discussion of arrhythmias has been purposely omitted "since their interpretation is not based on knowledge of the electrical phenomena associated with the heart beat." This might be a matter of dispute, since the pacemaking activity of the nodes and of ectopic foci are electrical phenomena, but it does illustrate how far electrocardiography has progressed since 1911 when, Sir Thomas Lewis wrote *Clinical Disorders of the Heart Beat*, which was completely concerned with disorders of rhythm.

Dr. Wolff's book is to be highly recommended for the libraries of all students of the subject.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

B.C.G. Vaccination in Theory and Practice. By J. Neville Irvine, D.M., M.A., B.Ch.Oxon., M.R.C.S.Eng., L.R.C.P. Lond., medical superintendent, Smith Isolation Hospital, physician to the Henley War Memorial Hospital and member of the editorial board of *Tuberculosis Index and Abstracts*. With a foreword by Konrad Birkhaug, M.Sc., M.D., chief of the B.C.G. Laboratory, New York State Department of Health. 8°, cloth, 130 pp. Springfield, Illinois: Charles C Thomas, 1950. $3.00.

In this monograph Dr. Irvine has reviewed the vast literature on a controversial subject, including the papers read at the first international congress on B.C.G., held in Paris in 1948. The material is well arranged, and the various chapters are documented with extensive bibliographies. The text is concluded with a world survey of B.C.G. vaccination. There are good indexes of subjects and authors, and the publishing is excellent. The monograph should be in all collections on tuberculosis.

The Cancer Bulletin. Vol. II, No. 1, January–February 1950. Texas edition, Texas Cancer Coordinating Council. 4°, paper, 24 pp. Houston, Texas: Medical Arts Publishing Foundation, 1950. Subscription rate: $4.00 per year in the United States, Canada and Mexico; $5.00 in foreign countries. Single copies: 75c.

This semipopular bulletin on cancer is well done and unusual in its treatment of the subject. The graphic illustrations are striking and designed for popular interest. In this number there is a description of the Hillsdale community plan for the practical detection of cancer. There are also two historical maps featuring persons of importance in the evolution of the knowledge of cancer from Aesculapius of ancient times to Rudolf Virchow (1821–1902).

World Surgery 1950. By Stephen A. Zieman, M.A., M.D., abstract and news editor, *Journal of the International College of Surgeons*, abstracter for *International Abstracts of Surgery* and *Surgery, Gynecology and Obstetrics*. 4°, cloth, 177 pp., with 53 illustrations. Philadelphia: J. B. Lippincott Company, 1950. $6.00.

This volume surveys the world literature on surgery for 1949, selected from the periodicals of all nations. The material is divided into sections, according to the systems of the body. There are good indexes of authors and subjects. The publishing is well done. This work is an addition to the prevailing progress reports that have sprung up in the United States during the past few years. It endeavors to cover the whole field of surgery.

Baby Talk. May, 1950. 4°, paper, 50 pp. New York: Ream Corporation, 1950. 25c.

This popular monthly magazine for mothers is now in its sixteenth year. It provides articles on all aspects of baby care.

Conference on Problems of Aging. Transactions of the Tenth and Eleventh Conferences, February 9-10, 1948, and April 25-26, 1949. Edited by Nathan W. Shock, chief, Section on Gerontology, National Heart Institute, National Institutes of Health and Baltimore City Hospitals. 8°, paper, 258 pp., with illustrations. New York: Josiah Macy, Jr., Foundation, 1950. $3.75.

These conferences, participated in by 26 specialists, cover a number of aspects of aging. The volume is well published, and complete sets should be in all large medical libraries.

Exhibitionism. By N. K. Rickles, M.D., senior consultant at the Veterans Administration Center, Los Angeles, consultant in psychiatry to the office of the Surgeon General, Medical Department, United States Army, and director of the Psychiatric Center of Seattle. 8°, cloth, 198 pp. Philadelphia: J. B. Lippincott Company, 1950. $5.00.

This monograph discusses exhibitionism in its various aspects, especially the etiology, diagnosis and treatment. The material is based on six years of special study. An appendix presents a number of case histories. The text is concluded with a bibliography, and there is a good index. The work should be in all collections on the subject.

The Yearbook of Psychoanalysis. Vol. V, 1949. Sandor Lorand, M.D., managing editor. 8°, cloth, 317 pp. New York: International Universities Press, Incorporated, 1950. $7.50.

This fifth volume of a standard serial contains 22 articles on varying aspects of psychoanalysis. The complete series should be in all collections on the subject.

Methods in Medical Research. Vol. II. Julius H. Comroe, Jr., editor-in-chief. 8°, cloth, 361 pp., with illustrations. Chicago: Year Book Publishers, Incorporated, 1950. $6.50.

This volume is the joint work of 60 contributors. The material is divided into three sections: methods of study of bacterial viruses; tests of pulmonary function; and assay of hormone secretions. Each chapter is documented with a bibliography of selected references. There are extensive indexes of subjects and names. It is proposed to issue further volumes in the series. The set should be in all medical libraries.

Proceedings of the First Clinical ACTH Conference. John R. Mote, M.D., editor. 8°, cloth, 607 pp., with illustrations. Philadelphia: Blakiston Company, 1950. $5.50.

This volume presents the 52 papers read at the first ACTH conference in Chicago, October 21 and 22, 1949. The persons attending were limited to actual investigators and their associates. The use of the hormone in various diseases is discussed. The volume is well published, except for the lack of an index, most essential in this type of book. It is recommended for all medical libraries.

Cancer: A manual for practitioners. Ernest M. Daland, M.D., chairman, The Committee on Publication. Second edition. 8°, cloth, 308 pp. Boston: American Cancer Society, Massachusetts Division, Inc., 1950.

In this second edition a manual first published in 1940 has been thoroughly revised and brought up to date. All the chapters have been rewritten, and several new ones added. The book is a composite work, the various chapters being written by specialists in their particular fields. The publishing is excellent, and the book should be in all collections on cancer.

NOTICES

ANNOUNCEMENTS

Dr. John J. Cranley, Jr., announces the opening of his office for the practice of general surgery in association with Dr. Robert R. Linton at 1180 Beacon Street, Brookline.

Drs. Benjamin Tenney, Jr., G. Douglas Krumbhaar and James F. Kenney, Jr., announce the removal of their offices to 203 Commonwealth Avenue, Boston.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

CONFERENCE PROGRAM

9–10 A.M.

Tuesday, February 20 — Trypsinated Red Blood Cells as an Immunological Technic. Dr. Martin C. Rosenthal.

Wednesday, February 21 — Review of Recent Advances in Medical Gynecology. Dr. Joseph Rogers.

Friday, February 23 — Studies with Radioactive Chromium. Dr. Seymour J. Gray.

Tuesday, February 27 — Cholesterol and Arteriosclerosis. Dr. John A. McGowan.

Wednesday, February 28 — Exfoliate Cytology. Dr. S. Charles Kasdon.

Conferences are held in the Pratt Lecture Hall.

All exercises are open to the medical profession.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

The regular meeting of the New England Society of Physical Medicine will be held at the Hotel Kenmore, Boston, on Wednesday, February 21, at 8 p.m. Dr. Robert T. Monroe, associate in clinical medicine, Harvard Medical School, and senior associate in medicine, Peter Bent Brigham Hospital, will speak on the subject "Rehabilitation in Old Age." A question period will follow.

Physicians, physical therapists, occupational therapists and students are cordially invited to attend.

BAY STATE HOSPITAL

The regular monthly staff meeting of the Bay State Hospital, Inc., will be held at the home of Dr. David J. Calicchio, 9 Keswick Street, Boston, on Friday, February 23, at 8:30 p.m. Dr. William E. Browne, surgeon-in-chief, Carney Hospital, will speak on the subject "Different Dressings for Acute Injuries of the Hand." Motion pictures will be shown and refreshments served.

EDWARD K. DUNHAM LECTURES

The Faculty of Medicine of Harvard University has announced that the following lectures will be delivered by Dr. Hugo Theorell, professor and director of the Medical Nobel Institute, Department of Biochemistry, Stockholm, Sweden, under the auspices of the Edward K. Dunham Lectureship for the Promotion of the Medical Sciences:

Tuesday, February 27. On the Rate of Incorporation of Isotopic Iron into Different Hemoproteins.

Thursday, March 1. Magnetochemical and Other Investigations on Myoglobin.

Tuesday, March 6. The Kinetics and Mode of Action of Alcohol Dehydrogenase.

These lectures will be held in the amphitheater of Building D, Harvard Medical School, at 5 p.m.

MASSACHUSETTS PHYSICIANS ART ASSOCIATION

A meeting of the Massachusetts Physicians Art Association will be held on Wednesday, February 28, at 8 p.m. Mr. Peter Pezzati, well known Boston painter, will entertain the members in his studio at 30 Ipswich Street, Boston.

PHI DELTA EPSILON LECTURE

The annual lecture of the Phi Delta Epsilon Fraternity will be given in the auditorium of the Beth Israel Hospital on March 13 at 8 p.m. Dr. Hans Selye, Director of the Institute of Experimental Medicine and Surgery at the University of Montreal School of Medicine, will speak on the subject "Recent Progress in the Study of the General Adaptation Syndrome."

All interested persons are invited to attend.

SEMINARS ON BLOOD CELLS AND PLASMA PROTEINS

The series of seminars on "Blood Cells and Plasma Proteins: Their state in nature" that commenced in February in Harvard Hall, Harvard College Yard, will continue through March and April. It is unfortunate that the notice of these important meetings was received too late for announcement of those that took place on February 1 and February 8. The program for March and April is as follows:

March 8. The Components of Human Blood Concerned with Immunity: Antibodies and the components of complement. Introductory presentation: Drs. Charles A. Janeway, John F. Enders and John L. Oncley. Discussion: Dr. Michael Heidelberger, professor of immunochemistry, Columbia University; Dr. William E. Ehrich, chairman, Department of Pathology, University of Pennsylvania.

March 15. The Red Cells of Human Blood: Their origin, properties and functions. Introductory presentation: Drs. John G. Gibson, II, Carl Walter, Charles P. Emerson, Jr., and Edward S. Buckley, Jr. Discussion: Dr. Orville F. Denstedt, professor of biochemistry, McGill University.

March 22. The Leukocytes and Platelets of Human Blood: Their origin, properties, and functions. Introductory presentation: Dr. James L. Tullis. Discussion: Dr. Charles A. Doan, professor of medicine, Ohio State University.

March 29. The Enzymes of the Blood Cells. Introductory presentation: Dr. Britton Chance, professor of biophysics, University of Pennsylvania and Dr. Orville F. Denstedt. Discussion: Dr. Eric G. Ball.

April 5. The Enzymes of Plasma. Introductory presentation: Drs. Douglas M. Surgenor, Ray K. Brown and Margaret J. Hunter. Discussion: Dr. Joseph S. Fruton, professor of physiological chemistry, Yale University School of Medicine.

April 12. The Lipoproteins of Human Blood. Introductory presentation: Drs. John L. Oncley and Frank R. N. Gurd. Discussion: Dr. J. Folch-Pi and Dr. John W. Gofman, assistant professor of medical physics, University of California.

April 26. The Interactions of Plasma Proteins with Metals, Carbohydrates, Drugs, and Other Organic Molecules. Introductory presentation: Drs. Walter L. Hughes, Jr., and Philip E. Wilcox. Discussion: Dr. George Scatchard, professor of physical chemistry, Massachusetts Institute of Technology.

AMERICAN COLLEGE OF SURGEONS

The fourth of a series of seven sectional meetings of the American College of Surgeons will be held in New Haven on March 16 and 17, with headquarters at Hotel Taft and Sterling Law Buildings' Auditorium, Yale University.

AMERICAN SOCIETY FOR THE STUDY OF STERILITY

The seventh annual meeting of the American Society for the Study of Sterility will be held at the Ritz Carlton Hotel, Atlantic City, New Jersey, on June 9 and 10, 1951.

Registration is in charge of the secretary-treasurer, Dr. Walter W. Williams, 20 Magnolia Terrace, Springfield, Massachusetts.

AMERICAN ACADEMY OF PEDIATRICS

The American Academy of Pediatrics will hold an areal meeting at the Netherland Plaza Hotel, Cincinnati, Ohio, on March 26–28.

The annual meeting will be held at the Royal York Hotel, Toronto, Ontario, Canada, on October 22–25, with seminars preceding the meeting on October 20 and 21.

SOCIETY MEETINGS AND CONFERENCES

FEBRUARY 19. New England Cardiovascular Society. Page 238, issue of February 8.

FEBRUARY 20. Massachusetts Trudeau Society. Page 238, issue of February 8.

FEBRUARY 20. South End Medical Club. Page 198, issue of February 1.

FEBRUARY 20–28. Joseph H. Pratt Diagnostic Hospital. Page 273.

FEBRUARY 21. New England Society of Physical Medicine. Page 273.

FEBRUARY 21. Bay State Society for the Crippled and Handicapped. Page 1066, issue of December 28.

FEBRUARY 23. Bay State Hospital. Page 273.

FEBRUARY 27. Norfolk District Medical Society. Page 629, issue of October 19.

FEBRUARY 27. Edward K. Dunham Lecture. Notice above.

FEBRUARY 28. Massachusetts Physicians Art Association. Notice above.

MARCH 1. Edward K. Dunham Lecture. Notice above.

MARCH 5–8. New Orleans Graduate Medical Assembly. Page 1018, issue of December 21.

MARCH 6. Edward K. Dunham Lecture. Notice above.

MARCH 7. Hampshire District Medical Society. Page 170, issue of July 27.

MARCH 8. Some Fundamental Indications for the Use of Forceps. Dr. M. Fletcher Eades. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

MARCH 8–APRIL 26. Seminars on Blood Cells and Plasma Proteins. Notice above.

MARCH 11–16. College of Medical Evangelists. Page 74, issue of January 11.

MARCH 13. Phi Delta Epsilon Lecture. Notice above.

MARCH 16 AND 17. American College of Surgeons. Notice above.

MARCH 21. A Demonstration of Pilot Wearers of Some of the Newer Devices in Prostheses. Dr. Augustus Thorndike. New England Society of Physical Medicine. Hotel Kenmore. 8 p.m.

MARCH 22. Hyman Morrison Lecture. Page 74, issue of January 11.

MARCH 26. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.

MARCH 26–28. American Academy of Pediatrics. Notice above.

MARCH 27. Norfolk District Medical Society. Page 629, issue of October 19.

APRIL 9–13. American College of Physicians. Page 296, issue of June 15.

APRIL 10. New England Society of Anesthesiologists. Page 512, issue of September 28.

APRIL 18. Physical Medicine and Rehabilitation in Psychiatry. Dr. Walter E. Barton. New England Society of Physical Medicine. Hotel Kenmore. 8 p.m.

APRIL 24. Norfolk District Medical Society. Page 629, issue of October 19.

APRIL 28. American Psychosomatic Society. Page 198, issue of February 1.

(*Notices concluded on page xv*)